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(54) Title: ELECTROLYTE SOLUTIONS AND *IN VIVO* USE THEREOF**(57) Abstract**

Electrolyte solutions which are useful in electrolyte and fluid therapy, parenteral nutrition, and dialysis. The Na:Cl ratio is normalized, plasma and cellular pH are normalized, and cellular co-factor ratios are normalized, in a manner which decreases toxicity over prior art solutions. The solutions employ at least one of the following near-equilibrium couples: (a) bicarbonate/CO₂; (b) 1-lactate/pyruvate; and (c) d-betahydroxybutyrate/acetoacetate.

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1 ELECTROLYTE SOLUTIONS AND IN VIVO USE THEREOF
DESCRIPTION

This invention lies in the field of in vivo techniques and compositions for replenishing fluid electrolytes and nutrients while regulating metabolic processes in living mammals.

State of the Art

The vital functions of highly developed organisms are closely dependent on the internal aqueous medium and on the maintenance in it of extreme constance of chemical and physical properties.

It has long been recognized that all animal intracellular and extracellular body fluids contain inorganic electrolytes, and that these electrolytes are involved in, and profoundly influence, various life processes.

Attempts to make artificial electrolyte fluids which may bathe tissues or be administered to the human blood stream have been known since about 1880, and, although modern analytical tools and procedures have clarified compositional details of blood electrolytes, the use of various aqueous electrolyte solutions for in vivo purposes in human medicine and related fields has been extant for approximately one hundred years.

Those inorganic electrolytes characteristically found in normal human blood serum at respective concentration levels above about 1 millimolar per liter of concentration are shown below in Table I. Also, for comparative purposes, in Table I are shown some representative compositions of various aqueous electrolyte solutions that have been previously prepared and used for in vivo purposes. In general, the philosophy behind the formulation of aqueous electrolyte solutions for in vivo use has been that such should mimic or closely resemble the chemical composition of electrolytes in blood and plasma. An electrolyte is a sub-

stance (usually a salt, acid or base) which in solution dissociates wholly or partly into electrically charged particles known as ions (the term is also sometimes used in the art to denote the solution itself, which has a high electrical conductivity than the pure solvent, e.g. water). The positively charged ions are termed cations while the negatively charged ions are termed anions. Strong and weak electrolytes are recognized. The dissociation of electrolytes is very markedly dependent on concentration: it increases with increasing dilution of the solution. The ions can be regarded as molecules in electrolyte solutions. Because of dissociation considerations, the term "sigma" or the greek letter for sigma ("Σ") is sometimes employed herein as a prefix to designate the total presence of a specified material, such as an electrolyte, whether or not all of the material is in an ionic form complexed with a heavy metal, or regardless of charge on the material in a given solution. A pair of brackets ([]) indicates the free concentration of the substance indicated as opposed to that bound to tissue components, such as proteins.

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SUBSTITUTE SHEET

Table I - Prior Art. Class Ia Solutions Containing 1 or 2 Cations, no Nutrients and No $\text{HCO}_3^-/\text{CO}_2$

Units	Normal	I. a. 1	I. a. 2	I. a. 3.
Plasma	Normal	Normal	Isotonic	
moles	N.E.J.M.	0.9% Saline	0.95% Saline	Na Lactate,
-----	283, 1285	U.S.	U.K.	Salt
L fluid	1970			
Na	136 - 145	155	162.5	160.3
K	3.5 - 5.0			
Ca	2.1 - 2.6			
free $[\text{Ca}^{2+}]$	[1.06]			
Mg	0.75 - 1.25			
free $[\text{Mg}^{2+}]$	[0.53]			
Eq Cations	142.7-153.2	155	162.5	160.3
Cl	100 - 106	155	162.5	160.3
HCO_3^-	26 - 28			
ΣPi	1 - 1.45			
SO_4^-	0.32 - 0.94			
L - lactate	0.6 - 1.8			52.0 (d,l)
pyruvate				
Lact/pyr			00	
D 3 OHbutyrate				
acetoacetate				
BHB/ acac				
acetate				
Other				
$\Sigma \text{Eq anions}$	128.7-139.4	155	162.5	160.3
Na/Cl	1.28 - 1.45	1.00	1.00	1.48
Glucose	3.9 - 5.6			
or others				
CO_2	0.99 - 1.39			
pH	7.35 - 7.45	5.5 - 6.5	5.5 - 6.5	~6.5
Σosm	285 - 295	310	325	321

Uses:

- I. a. 1. Most common U.S. I.V. electrolyte solution, *Merck Manual*. Causes hyperchloremic acidosis with $\text{Na}/\text{Cl} = 1.00$. See Black DAK. *Lancet* i, 353, 1952.
- I. a. 2. Used as "normal" saline in U.K. and Canada. *Geigy Handbook*.
- I. a. 3. Darrow et al. *J. Am. Med. Ass.* 143: 365, 432, 1944. Normal Na/Cl ratio but causes abnormalities.

Table I (Cont'd) - Prior Art. Class 1b. Solutions Containing 1 or 2 Cations, HCO_3^- , and No Nutrients.

Units	Normal	1. b. 1.
moles	Plasma M.E.M. 283, 1285	Isotonic NaHCO_3 Salt 1970
L fluid		

Na	136 - 145	160.3
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K	3.5 - 5.0	
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Ca	2.1 - 2.6	
free $[\text{Ca}^{2+}]$	[1.06]	

Mg	0.75 - 1.25	
free $[\text{Mg}^{2+}]$	[0.53]	

$\Sigma \text{mEq Cations}$	142.7-153.2	160.3
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Cl	100 - 106	108.3
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HCO_3^-	26 - 28	52
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ΣPi	1 - 1.45	
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SO_4^-	0.32 - 0.94	
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L - lactate	0.6 - 1.8	
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pyruvate		
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Lact/pyr		
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D & DHbutyrate		
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acetoacetate		
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BHB/ acac		
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acetate		
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Other		
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$\Sigma \text{mEq anions}$	128.7-139.4	160.3
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Na/Cl	1.28 - 1.45	1.48
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Glucose	3.9 - 5.6	
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or others		
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CO_2	0.99 - 1.39	
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pH	7.35 - 7.45	8.6
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ΣmOsm	285 - 295	321
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Uses:		
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1. b. 1. Darrow et al. *J. Am. Med. Ass.* 143: 365, 432, 1944. Use of Bicarbonate alone to correct Na/Cl ratio gives a solution with an abnormal pH, and one which will cause Ca^{2+} or Mg^{2+} added to the solution to precipitate as MgCO_3 or Ca CO_3 . Is the common alternative to Na lactate, salt; 1. a. 3.

Table I (Cont'd) - Prior Art. Class Ic Solutions Containing 1 or 2 Cations, with Non-ionic Nutrients.
 Typically 2.5%, 5%, 10%, 20% Glucose or Fructose in the U.S. and 2.62%, 5.25%, 10.5%, 20% Glucose or Fructose in the U.K.

Units	Normal Plasma mMoles L fluid	I. c. 1. 5% Dextrose 283, 1285 in H ₂ O, U.S. 1970	I. c. 2. 5.25% Dextrose in H ₂ O, U.K.	I. c. 3. Isotonic Glucose 2 + NaCl 1	I. c. 4. Glucose + NaLactate + NaCl	I. c. 10. 0 - 5 - W + 0.9% NaCl	I. c. 11. 10% Glucose + 0.9% NaCl	I. c. 12. 2.5% Glucose 0.45% NaCl in Electro- lyte 75	I. c. 13
Na	136 - 145			54.1	53.4	154	154	77	40
K	3.5 - 5.0							35	
Ca ²⁺ free [Ca ²⁺]	2.1 - 2.6 [1.06]								
Mg ²⁺ free [Mg ²⁺]	0.75 - 1.25 [0.53]								
Σ mEq Cations	142.7-153.2	0	0	54.1	53.4	154	154	77	75
Cl	100 - 106			54.1	56.1	154	154	77	47.5
HCO ₃ ⁻	- 26 - 28								
EPi	1 - 1.45								7.5H ₂ PO ₄
SO ₄ ²⁻	0.32 - 0.94								
L - lactate	0.6 - 1.8				17.3 (d,l)				20 (d,l)
pyruvate									
Lact/pyr					00				00
D B OHbutyrate									
acetoacetate									
B HB/ acac									
acetate									
Other									
Σ mEq anions	129.7-139.4	0	0	54.1	53.4	154	154	77	75
Na/Cl	1.28 - 1.45			1.00	1.48	1.00	1.00	1.00	0.34
Glucose or others	3.9 - 5.6	278	292	195	195	278	556	139	
CO ₂	0.99 - 1.39								278 (Fructose)
pH	7.35 - 7.45	6.5	6.5	6.5	6.5	6.5 - 6.5	6.5 - 6.5	6.5 - 6.5	
Σ osm	285 - 295	278	292	301	302	561	813	293	428
Use:									

1. c. 1. Most used I.V. solution in the U.S. *Merck Handbook*, 1966, p.1867. This is combined with NaCl in varying proportions so long as the osmolarity is not below 270 mOsm.
1. c. 2. Same solution in the U.K., where "isotonic" differs. *Geigy Handbook*, 1970, p. 334.
1. c. 3. *Geigy Handbook*, 1970, p. 334, has Na/Cl = 1.00
1. c. 4. *Geigy Handbook*, 1970, p. 334, has reasonable Na/Cl ratio but induces an abnormal redox state.
1. c. 10. through 1. c. 12. See *Facts and Comparisons* p. 51, Oct '81, Lippincott
1. c. 13. *Facts and Comparisons* p.52b Aug '83, Lippincott. Used in parenteral nutrition.

Table I (Cont'd) - Prior Art. Class Ia Solutions Containing 1 or 2 Cations, Nutrients, and $\text{HCO}_3^-/\text{CO}_2$.
None in prior art.

Units	Normal
moles	Plasma
-----	N.I.J.M.
-----	283, 1285
L fluid	1970

Na 136 - 145

K 3.5 - 5.0

Ca 2.1 - 2.6
free $[\text{Ca}^{2+}]$ [1.06]

Mg 0.75 - 1.25
free $[\text{Mg}^{2+}]$ [0.53]

$\Sigma \text{aEq Cations}$ 142.7-153.2

Cl 100 - 106

HCO_3^- 25 - 28

ΣPi 1 - 1.45

SO_4^- 0.32 - 0.94

L - lactate 0.6 - 1.9

pyruvate

Lact/pyr

D-B OHbutyrate

acetoacetate

BHB/ acac

acetate

Other

$\Sigma \text{aEq anions}$ 128.7-139.4

Na/Cl 1.28 - 1.45

Glucose 3.9 - 5.6
or others

CO_2 0.99 - 1.39

pH 7.35 - 7.45

ΣaO_2 285 - 295

Use

Table I - Prior Art. Class 2a Electrolyte Fluids Containing 3 or 4 Cations Suitable for Contacting Cells. Containing (Cont'd) No $\text{HCO}_3^-/\text{CO}_2$ and No Glucose; eg. after S.J. Ringer, *Physiol* 4: 29, 223, 1883.

Units moles L fluid	Normal Plasma H.E.J.K. 283, 1285 1970	2. a. 1. Ringer's Injection U.S.	2. a. 2. Lactated Ringer's	2. a. 3. Lactated Ringer's (Commercial)	2. a. 4. Acetated Ringer's U.S.	2. a. 5. Lact/Acet Ringer's	2. a. 10. Ionomol D-CM (Abbott)	2. a. 11. Plasmaalyte (Travenol)	2. a. 12. Isolyte S (McGaw) Polyionic 148(Cutter)
Na	136 - 145	147	129.8	130	130	140	139	140	140
K	3.5 - 5.0	4	5.4	4	4	10	12	10	5
Ca free [Ca ²⁺] [1.06]	2.1 - 2.6	2.5	0.9	1.5	1.5	2.5	2.5	2.5	2.5
Mg free [Mg ²⁺] [0.53]	0.75 - 1.25		1.0			1.5	1.5	1.5	1.5
Σ Eq Cations	142.7-153.2	156	139	137	137	158	158	158	148
Cl	100 - 106	156	111.8	109	109	103	108	103	98
HCO_3^-	26 - 28								
Σ Pi		1 - 1.45							
SO_4^-	0.32 - 0.94								
L - lactate pyruvate	0.6 - 1.8		27.8 (d,l)	28 (d,l)		27.5 (d,l)	50 (d,l)	8 (d,l)	
Lact/pyr			00	00		00	00	00	
D B DHbutyrate									
acetoacetate									
B HB/ acac									
acetate					28	27.5		47	27
Other									23 (gluconate) 148
Σ Eq anions	128.7-139.4	156	139	137	137	158	158	158	148
Na/Cl	1.28 - 1.45	0.94	1.16	1.19	1.19	1.36	1.29	1.36	1.43
Glucose or others	3.9 - 5.6								
CO_2	0.99 - 1.39								
pH	7.35 - 7.45								
Σ mOsm	285 - 295	309	276	272	272	312	312	312	294
Use:		I.V. fluid	I.V. fluid	I.V. fluid	I.V. fluid	I.V. fluid	I.V. electro	I.V. electro	I.V. elec
							-lyte	-lyte	-trolyte
							therapy	therapy	therapy
2. a. 1. Facts and Comparisons p50, Oct'81, Lippincott									
2. a. 2. Hartmann AF. <i>J. Am. Med. Ass.</i> 103: 1349, 1934.									
2. a. 3. Facts and Comparisons p50, Oct'81, Lippincott.									
2. a. 4. Facts and Comparisons p50, Oct'81, Lippincott.									
2. a. 5. Fox et al. <i>J. Am. Med. Ass.</i> 148: 827, 1952.									
2. a. 10. Facts and Comparisons p50, Oct'81, Lippincott.									
2. a. 11. Facts and Comparisons p50, Oct'81, Lippincott.									
2. a. 12. Facts and Comparisons p50, Oct'81, Lippincott.									

2E

Table I - Prior Art. Class 2a (Cont'd).

Units	Noreal Plasma mmoles L fluid	2. a. 13. H.E.J.M. 283, 1285 1970	2. a. 14. Isolyte E (McGaw)	2. a. 15. Delbecco's Phosphate Saline	Kreb's Ringer Phosphate
Na	136 - 145	140	152.2	150.76	
K	3.5 - 5.0	10	4.17	5.92	
Ca	2.1 - 2.6 free [Ca ²⁺] [1.06]	2.5	0.9	2.54	
Mg	0.75 - 1.25 free [Mg ²⁺] [0.53]	1.5	0.49	1.18	
≥ aEq Cations	142.7-153.2	158	159.15	164.12	
Cl	100 - 106	103	140	131.51	
HCO ₃	26 - 28				
≥ Pi	1 - 1.45		9.83	17.38	
SO ₄	0.32 - 0.94		0.48	2.35	
L - lactate	0.6 - 1.8				
pyruvate					
Lact/pyr					
D B OHbutyrate					
acetoacetate					
B HB/ acac					
acetate		49			
Other		4 citrate			
≥ aEq anions	128.7-139.4	158	159.18	165.15	
Na/Cl	1.28 - 1.45	1.40	1.08	1.15	
Glucose or others	3.9 - 5.6				
CO ₂	0.99 - 1.39				
pH	7.35 - 7.45		7.4	7.4	
≥ aOs	285 - 295	315	308	311.16	
Use:	I.V. electrolyte therapy	Usually tissue culture, sometimes cardiac surgery	Biochemical experiments		

2. a. 14. Delbecco R, Vogt M. *J Exp Med* 1954; 99: 167 - 1822. a. 13. *Facts and Comparisons* Oct, 1981, p.50, Lippincott, St.Louis2. a. 15. Krebs HA. *Hoppe S Z Physiol Chem* 1933; 217: 193

Table I - Prior Art, Class 2b Solutions Containing 3 or 4 Cations, $\text{HCO}_3^-/\text{CO}_2$, and No Glucose or Other Non-Ionic Nutrients.

Units	Normal	2. b. 1.
samples	Plasma	Krebs
	K.E.J.M.	Henseleit
-----	283, 1285	
L fluid	1970	

Na	136 - 145	143
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K	3.5 - 5.0	5.9
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Ca	2.1 - 2.6	2.5
free $[\text{Ca}^{2+}]$	$[1.06]$	

Mg	0.75 - 1.25	1.2
free $[\text{Mg}^{2+}]$	$[0.53]$	

$\Sigma \text{ aEq Cations}$ 142.7-153.2 156.3

Cl	100 - 106	127.8
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HCO_3^-	26 - 28	25
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ΣPi	1 - 1.45	1.18
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SO_4^-	0.32 - 0.94	1.18
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L - lactate	0.6 - 1.8	
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pyruvate

Lact/pyr

D & OHbutyrate

acetoacetate

BHB/ acac

acetate

Other

$\Sigma \text{ aEq anions}$ 128.7-139.4 157.3

Na/Cl	1.28 - 1.45	1.12
-------	-------------	------

Glucose	3.9 - 5.6	
---------	-----------	--

or others

CO_2	0.99 - 1.39	1.24
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pH	7.35 - 7.45	7.4
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$\Sigma \text{ osm}$	285 - 295	308
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Use:	Multiple Biochemical Uses
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2. b. 1. Krebs HA, Henseleit K. *Hoppe-Seyler's Z Physiol Chem* 1932; 210: 33-66. This is the second major advance in fluids, after S.J. Ringer, *Physiol* 1883; 4: 29, 223. This fluid became the basis for most tissue culture "balanced salt mixtures," was used in dialysis. It is known to contain twice too much Ca and Mg. It also has an abnormal Na/Cl ratio which Krebs himself unsuccessfully attempted to correct in 1950. (See Krebs HA. *B & A* 1950; 4: 249- 269, or Table I class 2d.)

Table I - Prior Art. Class 2c Solutions Containing 3 or 4 Cations, No $\text{HCO}_3^-/\text{CO}_2$ to Which is Added Non-Ionic Nutrients.

Units	Normal Plasma mmoles 283, 285	2. c. 1. N.E.J.N. Ringer's + 5%Glucose	2. c. 2. Lactated + 2.5%Glucose	2. c. 3. Lact-Ringer + 2.5%Glucose	2. c. 4. Acetated Ringer's + Glucose	2. c. 5. Ionosol B (Abbott)	2. c. 6. Dianeal (Travenol)	2. c. 7. Peritoneal Dialysis + 4.25%Glucose (Am. McGraw)
L fluid	1970							
Na	136 - 145	130	65	130	57	141	141.5	132
K	3.5 - 5.0	4	2	4	25			4
Ca free [Ca ²⁺] [1.06]	2.1 - 2.6	1.5	0.75	1.5		1.75	2.0	1.875
Mg free [Mg ²⁺] [0.53]	0.75 - 1.25				2.5	0.75	0.75	0.75
Σ mEq Cations	142.7-153.2	137	68.5	137	87	146	147	141
Cl	100 - 106	109	55	109	49	101	102.5	106
HCO_3^-	26 - 28							
Σ Pi	1 - 1.45				6.5 H_2PO_4^-			
SO_4^-	0.32 - 0.94							
L - lactate	0.6 - 1.8	29(d,1)	14(d,1)		25(d,1)	45(d1)		35(d,1)
pyruvate								
Lact/pyr		00	00		00	00		00
D B OHbutyrate								
acetoacetate								
B HB/ acac								
acetate				29			44.5	
Other								
Σ mEq anions	128.7-139.4	137	69	137	87	146	147	141
Na/Cl	1.28 - 1.45	1.19	1.18	1.19	1.16	1.40	1.38	1.25
Glucose or others	3.9 - 5.6	278	139	278	278	83	236	236
CO_2	0.99 - 1.39							
pH	7.35 - 7.45					7.5-8.5	7.5-8.5	7.5-8.5
Σ osm	285 - 295	524	263	523	443	366	510	494
Use:		I.V. fluid nutrition & for de- hydration	I.V. fluid 2.c.l.	same as 2.c.l.	Parenteral Nutrition	Peritoneal Dialysis	Peritoneal Dialysis	Peritoneal Dialysis

2. c. 1. Multiple Manufacturer's Facts and Comparisons p.52, Oct '81
 2. c. 2. Multiple Manufacturer's Facts and Comparisons p52, Oct '81
 2. c. 3. Multiple Manufacturer's Facts and Comparisons p52, Oct '81
 2. c. 4. (Abbott) Facts and Comparisons p52b, Aug '83
 2. c. 5. (Travenol) Facts and Comparisons p704, Oct '82
 2. c. 6. (American McGraw) Facts and Comparisons p704, Oct '82
 2. c. 7. (Travenol) Facts and Comparisons p704, Oct '82

Table I - Prior Art. Class 2d Solutions Containing 3 or 4 Cations, Plus Non-Ionic Nutrients and $\text{HCO}_3^-/\text{CO}_2$

Units moles L fluid	Normal Plasma H.E.J.M. 283, 1285 1970	2. d. 1. Krebs Serum Substitute	2. d. 2. Tyrode's Solution I (Schimassek)	2. d. 3. Tyrode's Solution	2. d. 4. Locke's Solution
Na	136 - 145	141	151.54	150.1	157.57
K	3.5 - 5.0	5.93	5.9	5.9	3.57
Ca free $[\text{Ca}^{2+}]$	2.1 - 2.6 [1.06]	2.54	1.8	1.8	2.16
Mg free $[\text{Mg}^{2+}]$	0.75 - 1.25 [0.53]	1.18	0.45	0.45	0
$\Sigma \text{mEq Cations}$	142.7-153.2	154.37	162.07	160.5	165.46
Cl	100 - 106	104.9	147.48	147.48	163.92
HCO_3^-	26 - 28	24.9	11.9	11.9	3.57
ΣPi	1 - 1.45	1.23	1.22	1.22	—
SO_4^-	0.32 - 0.94	2.36			
L - lactate	0.6 - 1.8		1.33		
pyruvate		4.9	0.09		
Lact/pyr			14.8		
0.0 BHbutyrate					
acetoacetate					
0.0 HB/acac					
acetate					
Other		2.45 glutamate 5.4 fumarate			
$\Sigma \text{mEq anions}$	128.7-139.4	154.47	162.81	161.6	167.49
Na/Cl	1.28 - 1.45	1.35	1.03	1.02	0.96
Glucose or others	3.9 - 5.6	9.2	5.45	5.6	5.6 - 13.7
CO_2	0.99 - 1.39	1.0	1.17		
pH	7.35 - 7.45	7.4	7.1	7.1	?
ΣmOsm	285 - 295	308.2	328	318.3	336
Use:		Artificial Serum for Tissue Slices Normal Na/Cl	Liver Perfusion		

2. d. 1. Krebs HA. *B.B.A.* 4: 249 - 269, 1950. Not used *in vivo* but presented for comparison of composition.
2. d. 2. Tyrode's solution as modified for liver perfusion by Schimassek H, *Biochem Z* 336: 460, 1963. Not used *in vivo* but presented to show prior art in composition. Same for 2. d. 3, Tyrode's, and 2. d. 4, Locke's.
2. d. 3. Tryrode MV, *Arch int Pharmacodyn Ther* 20: 205 - 223, 1910.
2. d. 4. Locke FS, *Zeitbl Physiol* 14: 670 -672, 1900.

1 Contemporarily, a large number of different
aqueous electrolyte solutions are prepared, sold in com-
merce, and used as in vivo fluids, such as for electro-
lyte and fluid replacement, parenteral nutrition, and
5 dialysis (both hemo-and peritoneal).

Even a cursory examination of Table I will confirm
the medical dicta that "plasma is an unmakable solution".
The solutions listed in Table I illustrate this belief.
The essential problem is that plasma contains, in addi-
10 tion to major inorganic electrolytes, trace quantities
of various electrolytes plus various metabolites includ-
ing plasma proteins. In practice, it has not been possible
to construct synthetically a replication of plasma
because of its complexity. Blood, extracellular fluid,
15 and even plasma can be regarded as tissues.

In most prior art electrolyte solutions, the con-
centration of chloride anions (Cl^-) is higher than in
human plasma or serum. For example, the Krebs Henseleit
solution (see Table I) contains a concentration of Cl^-
20 which is about 20% higher than in human serum. This
anion gap, that is, the difference between the positive
cations and the negative anions, is now known to be due
largely to the anionic metabolites in normal plasma
plus the contribution of acidic amino acid groups found
25 on plasma proteins. Referring to Table I, it is seen
that the total positive cations in plasma is 142-154
meq/l while the total anions is only about 128-137 meq/l
leaving a deficit of about 14-17 meq/l of anions. For
convenience, the anion gap in human plasma can be ex-
30 pressed as the ratio of sodium cation milliequivalents
per liter to chloride anion milliequivalents per liter.

From Table I, it is clear that the Krebs Serum
substitute (Krebs, H.A. Biochem, Biophys. Acta 4, 249-
269, 1950) comes closest to approximating the electro-
lyte composition of human plasma. In this solution,
35

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1 Krebs attempted to correct the excessive Cl^- content
in Krebs Henseleit solution (Hoppe-S. Z. Physiol. Chem.
210, 33-66, 1932) using metabolic experiments with tissue
slices. Because of the law of electrical neutrality,
5 Na^+ cannot be added to a solution without some anion
(such as Cl^-) being added also; the sum of cations and
anions must be equal in any solution. In his 1950
attempt, Krebs chose pyruvate $^-$, l-glutamate $^-$, and
fumarate $^{2-}$ as anions to be added.

10 An alternative to Krebs selection of anions came
about at the same time. In 1949, the use of high concen-
trations of acetate as a metabolizable organic anion was
advocated (Mudge G.H., Mannining J.A., Gilman A.;
15 Proc. Soc. Exptl. Biol. Med. 71, 136-138, 1949). This
idea led in 1964 to the advocacy of the use of 35-45mM
(millimolar) acetate in commercial hemodialysis
fluids (Mion C.M. Hegstrom R.M., Boen S.T., Scribner
B.H.; Trans. Am. Soc. Artif. Internal Organs 10, 110-113,
1964).

20 In addition to the above organic anions, the current
reference work "Facts and Comparisons" indicates various
commercial electrolyte fluids which contain lactate
anion.

25 All of the prior art electrolyte solutions (with
or without nutrients) as exemplified in Table I are now
believed to lead to undesirable and pathological conse-
quences particularly through extended usage. As regards
acetate, editorials recently appearing in the British
30 Medical Journal, 287, 308-309, 1983) present evidence
that acetate leads to fatigue, nausea, malaise, sudden
hypotension, increased atherosclerosis, hypoventilation,
and hypoxia. Also, the originator of acetate dialysis now
advocates its use only in "healthy" patients (Pagel
M.D., Ahmed S. Vizzo J.E. and Scribner B.H.; Kidney Int.
35 21, 513-518, 1982).

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1 Krebs choice of glutamate⁻ and fumarate²⁻ is incor-
rect because these anions do not penetrate cell membranes
in a predictable manner, but, like citrate³⁻, exhibit
severe gradients of six fold or greater between plasma
H₂O and cell H₂O. The alternate use of d,l-lactate⁻
5 (Hartmann AF. J Am Med Asso 103 1349-1354, 1934) is now
known to induce severe abnormalities, particularly coma
at levels far below the 28 to 35 mM d,l-lactate contained
in these solutions (Oh MS et al, N. Eng J Med 301 249
10 251, 1979; Stolberg L, et al N Eng J Med 306: 1344-1348.
15 1982; Ballabriga A, et al Helv Paediatr Acta 25:25-34,
1970) in to the induction severe abnormalities in redox
and phosphorylation state induced by the use of l-lactate
alone. The use of gluconate⁻ induces abnormalities
in the hexosemonophosphate pathway. Indeed, all previous
15 used organic ions violate the "safe entry points" or
the normal Na:Cl ratio as herein defined.

20 In addition to the use of d,l-lactate, gluconate,
fumarate, glutamate, pyruvate, and citrate anions in
current commercially available prior art electrolyte
fluids, and wherein such anions are typically employed
at levels above those found in the (plasma or serum)
of healthy humans, many such prior art commercial fluids
also employ high levels of nonionic metabolites, such as
25 fructose and glycerol, which induce separate redox
state and phosphorylation potential abnormalities in
phosphorylation potential with rapid destruction of
liver purine nucleotides and their release into blood
sometimes leading to renal shutdown due to uric acid
30 deposition in the kidneys (see Woods H.F., Eggleston
L.V. and Krebs H.A.: Biochem. J. 119, 501-510, 1970).
Fructose in plasma above 0.2mM must be considered to
violate the "safe entry point". Likewise, use of intra-
venous glycerol at levels above 5mM/l as currently
35 practiced leads, in tissue containing glycerol kinase,

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1 such as kidney and liver, to accumulation of 10 mM
glycerol phosphate (over 100 times normal). See Bruch
H.B. et al.: J. Biol. Chem. 257, 3676-3679, 1982).

5 In addition to failing to solve the anion gap
problem (or to provide a normal milliequivalent ratio
of sodium cation to chloride anions) without causing
profound and adverse physiological effects (including
disruption of normal redox state and normal phosphoryl-
ation potential), many prior art aqueous electrolyte
10 solutions for in vivo usage fail to have a pH which
approximates the pH of mammalian intracellular and
extracellular fluids, especially plasma or serum.

Mammalian systems normally operate at temperatures
between about 37-38°C where, by common thermodynamic
15 convention, neutral pH is taken to be about 7 at 25°C.
It is clear that changes in pH, (the negative log
10 of $[H^+]$ concentration) necessarily affect the
fundamental energetic relationships occurring in
living cells. Also, enzymes have sharply defined ranges
20 of $[H^+]$ concentration in which they perform their
catalytic functions in a normal manner. Deviation of
mammalian plasma pH down to 6.9 or above 7.7 from its
normal range of 7.35 - 7.45 is therefore fatal to most
mammalian organisms. Massive changes in the cellular
25 redox and phosphorylation states also disorder cellular
homeostasis.

The pH of human plasma is normally maintained by
the human body in the range from about 7.35 to 7.45
while the pH of human cellular cytoplasm is about 7.2
30 (see Veech et al in J. Biol. Chem. 254, 6538-6547, 1979).
If blood pH drops to 6.8 in man, then death ensues from
cardiac arrest, and if blood pH increases to above pH
7.7, then death ensues from convulsions.

35 The major chemical system maintaining body pH
within this narrow normal range is the $[CO_2]/[HCO_3^-]$

1 buffer system. The $[CO_2]$ of blood is maintained minute
to minute by a portion of the mammalian brain called the
respiratory center which senses brain cell pH and adjusts
the depth and speed of respiration to change pH by increas-
5 ing or decreasing $[CO_2]$ according to the famous Henderson
Hasselbalch equation (Henderson L.J., Silliman Lectures,
Yale U. Press, New Haven, 1928).

Even though pH is thus seen to be a critical factor
in mammalian blood, many commercial electrolyte solutions
10 as administered have pH values which deviate substantially
from normal. Others give excessive Cl^- relative to Na^+
which results in hyperchloremic acidosis, (Black D.A.K.:
Lancet i 305-12, 1953), or give organic anions in a
15 manner which causes measurable deviations from normal
in the metabolic processes of the cell. Also, many
commercially available electrolyte solutions contain
no carbon dioxide which can result in a loss of
respiratory drive and consequent hypoxia in patients.

The compositions and methods of the present inven-
20 tion overcome the above indicated prior art problems.
These compositions and methods employ definite ratios
of $[bicarbonate^-]/[carbon\ dioxide]$, $[l-lactate^-]/$
 $[pyruvate^-]$, and $[d-beta hydroxybutyrate^-]/[acetoacetate^-]$.
Each of these mixtures constitute a near equilibrium
25 couple which is known to be a normal constituent of
mammalian plasma. While each of these pairs of
components has been previously employed at least on a
laboratory basis in solutions used for animal (mammalian)
experiments, these mixture pairs have never previously
30 been used in an electrolyte solution to obtain a normal
 $Na:Cl$ milliequivalent ratio or to solve the anion gap
problem.

All previous electrolyte solutions, and plasma
substitutes, induce severe and measurable pathogenic
35 abnormalities and no prior art electrolyte solution or
plasma substitute has both (a) employed at least one

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1 of the three mixture pairs of this invention and (b) achieve a normal Na: milliequivalent ratio as taught herein. Thus, for example, the Krebs Henseleit solution contains the $[\text{HCO}_3^-]/[\text{CO}_2]$ buffer system (but contains 5 excessive chloride ions). Schimassek (Schimassek H.; Bio. Chem. Z. 336, 460, 1963) added about normal blood levels of lactate and pyruvate to what is essentially Tyrode's solution (see Tyrode, M.J.: Arch. Int. Pharmacodyn 20, 205, 1910) containing 2.5% albimin in an attempt 10 to create a physiological solution for perfusion. It should be noted that Schimassek added 1.33mM/L D-L-lactate, which is definitely abnormal (see normal blood lactate levels shown in Table 1). Further, the Na^+ of 151mM/l and Cl^- of 147.5mM/l in Schimassek's modified 15 Tyrode's solution approximates the concentration of 155mM/l Na and 155mM/l Cl^- in so-called normal (0.9%) saline, the most widely used electrolyte infusion solution, and thus obtained a grossly abnormal Na:Cl milliequivalent ratio of about 1.24 - 1.45 with a mean of about 1.38. 20 Infusions of electrolyte solutions with a Na:Cl milliequivalent ratio of less than about 1.38 have long been known to cause hyperchloremic acidosis in the treated organism. (See Levinsky N.G. in Harrison's Textbook of Medicine pp 230-236, McGraw-Hill, N.Y., 1983). It 25 is the attempt to avoid this problem that leads to the wide use of such solutions as Ringer's lactate or acetate dialysis fluids which overcome the Na:Cl ratio problem, but which in turn create gross abnormalities of other types. It is the attainment of a normal Na:Cl milliequivalent ratio in a manner which avoids the pathological consequences inherent in all currently known or 30 practiced methods which is a major part of the invention herein disclosed.

35 The making of a Krebs Henseleit electrolyte solution (or other prior art electrolyte solution) and the

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1 incorporation thereinto of a mixture of L-lactate and
2 pyruvate anions, or of a mixture of D-betahydroxybutyrate
3 and acetoacetate anions did not, and could not, result
4 in the making of an electrolyte solution wherein the
5 anion gap problem was overcome (or wherein the milli-
6 equivalent ratio of sodium cations to chloride anions
7 was normalized), in accordance with the teachings of the
8 present invention, because each of such resulting solu-
9 tions would still contain excessive chloride anions and
10 so would inevitably cause hyperchloremia if and when
used in human or mammalian therapy.

In general summary, the prior art describes a series
15 of electrolyte solutions typically of about 270-320
milliosmoles (or higher) comprised of: (a) 1 to 4
metallic cations of sodium, potassium, magnesium, and
calcium in amounts greater than 0.5mM/L, (b) 1 to 5
inorganic anions of chloride plus also HPO_4^{2-}),
(c) 0 to several organic carboxylic or bicarbonate
anions, (d) 0 to 5 nonionic materials in concentrations
of greater than about 0.5mM/L from the group comprising
CO₂ gas, glucose, urea, glutamine, and others,
and (e) sometimes one or more high molecular weight
substances, such as albumin, hemocel, and the like.
None of these solutions, for the reasons herein above
20 explained, either normalize the milliequivalent ratio
of Na:Cl at all, or normalize this ratio without
causing profound and adverse physiological consequences.
In the present invention, there are provided processes
25 and compositions of a complex fluid nature for in vivo
usage which can substantially completely eliminate
all of such prior art problems. While the components
of these new solution compositions are known solution
components, no one has heretofore formulated the
solutions of the present invention which not only
30 tend to achieve a normal plasma milliequivalent ratio
35

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1 of sodium cations to chloride anions, but also tend to
achieve a normalization of plasma pH and a normalization
of the cellular redox state and the cellular phosphoryla-
tion potential. Also, these new solutions permit one
5 to avoid usage of the previously employed carboxylic
anions, as acetate, or lactate alone, which cause
adverse effects.

BRIEF SUMMARY OF THE INVENTION

This invention relates to processes for
10 accomplishing electrolyte and water therapy while simulta-
neously normalizing blood composition in a mammal
(including man) by introducing in a physiologically
effective amount by any means, including parenterally,
(intravenously), intra-arterially, intramuscularly,
15 intravascularly, and the like, by dialysis, or orally,
and the like into such mammal an aqueous solution wherein:

- (a) the ratio of sodium cation milliequivalents per
liter to the chloride anion milliequivalents
per liter are so selected as to tend to produce
20 the range found in normal mammalian blood plasma,
- (b) there is a physiologically effective amount of
at least one near equilibrium couple selected
from the group consisting of
25 (1) bicarbonate⁻ and carbon dioxide,
(2) l-lactate⁻ and pyruvate⁻, and
(3) d-betahydroxybutyrate⁻ and acetoacetate⁻, and
- (c) the pH ranges from 5 to 9.

This invention further relates to physiologically
compatible aqueous salt solutions for mammalian (includ-
30 ing human) administration which contain such a ratio
of sodium to chloride and which incorporate near-equili-
brium couple(s).

This invention provides electrolytes of the class
indicated wherein physiologically normal concentrations
35 of the divalent cations Mg^{2+} and Ca^{2+} may be included

1 without precipitation. No one has previously made solutions for in vivo use which contain the correct $\text{Na}^+ \text{Cl}^-$ ratio and which also contain the physiologically normal respective amounts of Mg^{2+} and Ca^{2+} .

5 When used for mammalian administration in accord with the present process teachings, such a solution:

- (a) tends to maintain and normalize in plasma the milliequivalent ratio of sodium cations to chloride anions in the normal range, and
- 10 (b) tends to maintain and normalize plasma pH, and
- (c) tends to maintain and normalize the redox state and the phosphorylation potential.

15 One (first) class of such solutions characteristic-ally utilizes (contains) an inorganic class of anions comprised of chloride and bicarbonate. These solutions have a physiological pH which is broadly in the range from about 5 to 9, and preferably in the range from about 6.9 to 8.6, and more preferably in the range from about 20 7.35 to 7.45, and most preferably is about 7.4 (for human use). Dissolved carbon dioxide is also present in these 25 solutions. When administered, these solutions not only tend to maintain the treated mammal's normal blood (and plasma) ratio of sodium to chloride, but also tend to set (regulate) the treated mammal's blood (plasma) pH at a normalized value. In addition the treated mammal's redox state and phosphorylation potential tend to be normalized.

30 Another (second) class (preferred) of such solutions characteristically utilizes (contains) chloride anions and a class of carboxylate anionic mixture couples comprised of at least one member from the group consisting of (a) a mixture of l-lactate⁻ anions and pyruvate⁻ anions, (b) a mixture of d-betahydroxybutyrate⁻ anions and acetoacetate⁻ anions, and (c) a mixture of both (a)

1 and (b). These solutions have a physiological pH which
is as above defined in connection with such (first)
class of solutions. When administered, these solutions
not only tend to maintain the treated mammal's redox
5 state within a normal range, but also tend to maintain
that mammal's phosphorylation potential within a normal
range.

Another (third) class (more preferred) of such solu-
tions characteristically utilizes (contains) both chloride
10 anions, and bicarbonate/carbon dioxide mixture, as in
such (first) class of solutions, but also utilizes
(contains) such class of carboxylate anionic couples,
as in such (second) class of solutions. When admini-
stered, these solutions achieve the above indicated
15 effects obtained from the use of such (first) class of
solutions and the above indicated effects obtained from
the use of such (second) class of solutions.

The specified milliequivalent ratio of sodium to
chloride in normal mammalian blood generally is believed
20 to be in the range from about 1.24:1 to 1.47:1. In
the case of a normal human adult, this range is now
believed to extend (based on published information)
from about 1.24:1 to 1.45:1 and preferably from about
1.33:1 to 1.42:1 and most preferably from about 1.36:1
25 to 1.42:1. These ratios of $\text{Na}^+:\text{Cl}^-$ are typically employed
in solutions used in the practices of this invention.
Ratios above 1.47, i.e. from about 1.47 to about 1.6 can
be used within the spirit and scope of this invention as
when it is the physician's conscience intention to create
30 an abnormal $\text{Na}^+:\text{Cl}^-$ ratio as, for example, to create an
excess of alkali reserve; however, such higher ratios
are generally not presently preferred for general usage.
In the case of dialysis fluids or to create an alka-
lotic condition in a cell or to correct an existent
35 acidosis, this $\text{Na}^+:\text{Cl}^-$ ratio could range from a normal
value (about 1.24 to 1.45) to about 1.6.

1 In using these couples, the important factor is
the ratio of the concentration of [product] / [reactant]
(see Eqns 0, 1,2,3,4,5 & 7 hereinbelow). The absolute
concentration becomes important in affecting the chemical
5 activity of water (e.g. the osmotic pressure).

10 The total quantity, or sum (sigma), of each of
the couples (bicarbonate / CO_2 , l-lactate / pyruvate,
and d-betahydroxybutyrate / acetoacetate) present in a
solution of this invention can range from 0 to about 465
15 mMoles/liter of solution. However, in routine situa-
tions, the quantity of each couple commonly ranges from
0 to about 25 to 60 mMoles/liter.

20 Preferably, the ratio of bicarbonate milliequivalents
per liter to dissolved carbon dioxide milliequivalents
15 per liter in a solution of this invention can range
from about 0.1:1 to 55:0.1 and preferably 11:1 to 24:1.
More preferably, such total ranges from about 10 to 45
mM/l and such ratio ranges from about 18:1 to 26:1,
and still more preferably such total ranges from about
25 23 to 35 mM/l while such ratio ranges from about 19:1
to 21:1. A ratio of 19.95 for $[\text{HCO}_3^-]/[\text{CO}_2]$ gives a pH
7.4, which is presently particularly preferred.

25 Preferably, the ratio of l-lactate anion milli-
equivalents per liter to pyruvate anion milliequivalents
per liter in a solution of this invention can range from
about 20:1 to 1:1. Preferably, such total quantity
ranges from about 0.5 to 10 mM/l and such ratio ranges
from about 3:1 to 15:1, and more preferably such total
quantity ranges from about 2 to 8 mM/l while such ratio
30 ranges from about 5:1 to 12:1.

35 Preferably, the ratio of d-betahydroxybutyrate anion
milliequivalents per liter to acetoacetate milliequivalents
per liter in a solution of this invention can range from
about 6:1 to 0.5:1. Preferably, such total ranges from
about 1 to 10 mM/l and such ratio ranges from about 4:1 to

1 1:1, and more preferably such total ranges from about 2
to 5mM/l while such ratio ranges from about 3:1 to 1.5:1.

5 By the term "milliequivalent ratio" as sometimes
used herein, reference is had the ratio of milliequivalents
per liter of one substance to milliequivalents per liter
of another substance in an aqueous medium.

10 One of the three near equilibrium couples employed
in the practice of this invention (the bicarbonate /
carbon dioxide couple) tends, as used in this invention,
15 to regulate the concentration of hydrogen ions in blood
(plasma) and in the treated mammal's cells, and each one
of such couples tends to normalize the redox state of
each of the three pyridine nucleotide couples. The
phosphorylation potential also tends to be normalized.
Also, each such near equilibrium couple when used as
herein described constitutes a safe entry point into
the metabolic system of a mammal.

20 By the term "safe entry point" as used herein refer-
ence is generally had to a metabolite which, in living
tissue or cells:

- (1) does not cause a massive buildup of one or
more of intermediate cellular metabolites,
- (2) does not cause a severe disruption of any one
of the controlling nucleotide ratios in a
25 living cell,
- (3) can be added to a physiological system of a
living mammal at a concentration level which is
greater than that which is found normally in
such system (such as blood plasma of a fasting
30 mammal) without causing any appreciable
distortion in metabolism and without causing any
pathological conditions to arise, and
- (4) may be found in normal variants of the
physiological state as when the total of d-
35 betahydroxybutyrate plus acetoacetate reaches

1 a level of about 8 to 10 mM/l in three- day
fasting man, or the total of 1-lactate plus
pyruvate rises to a level of about 5 to
6 mM/l in a jogging normal man.

5 Further, each such above described near equilibrium
couple in this invention exhibits a distribution or
permeability between intracellular fluid and extra-
cellular fluid such that the ratio of the concentrations
in, respectively, intracellular fluid to extracellular
10 fluid ranges from about 1.0:1 to 1.5:1 in most all
mammalian cells.

15 These respective three pairs of permeant mono-
carboxylate near equilibrium couples are unique among
metabolites in being osmotically neutral in respect
to the water in intracellular and extracellular space.
20 Administration of these three couples, as their appro-
priate cationic salts (individually or in some combina-
tion with one another as taught herein) necessarily re-
sults in no net change in the distribution of water
25 between intracellular and extracellular spaces in most
tissues. By administration of varying ratios of these
couples, however, the physician may control the distri-
bution of water by varying the redox state and hence the
phosphorylation state as described in equation 7 herein
30 below. Osmotically active substances incorporated with
the solutions of this invention preferably should each
constitute a safe entry point. For example, glucose
above 13mM/l is higher than ever occurs under normal
physiological conditions in a healthy man. Use of
35 glucose above 13mM/l (as in the widely used 5% glucose
solution) as a calorie source is, apart from consideration
of the source of pathology, and apart from the carbox-
ylate couples, considered herein to be an acceptable
source of calories. The extreme ability of the
mammalian body to regulate its glucose metabolism makes

1 it far to be preferred over other possibly nonionics, such as fructose or glycerol, which enter the metabolic system in an uncontrolled manner causing pathologic changes such as are already referenced, and so such are not
5 safe entry points.

Characteristically, a solution used in the practice of this invention can contain from about 1 to 2400 millimoles per liter of sodium cations, but, in routine situations, commonly ranges from about 120 to 170 mM/l
10 and more preferably from about 129 to 163.5 mM/l and most preferably from about 136 to 145 mM/l.

In addition, a solution contains sufficient chloride anions to produce a milliequivalent ratio of sodium cations to chloride anions in the range above defined.

15 Optionally, in addition to sodium, a solution of this invention can contain one or more of the following additional metallic cations each in a respective quantity as below indicated:

Table II

cation	Quantity range (millimoles per liter)		
	broad	preferred	more preferred
potassium	0 - 90	0 - 40	0 - 5
calcium	0 - 60	0 - 10	0 - 1.5
25 magnesium	0 - 15	0 - 10	0 - 1

30 Optionally a solution of this invention can have additionally incorporated (dissolved) therein from 0 to about 2400 millimoles per liter of at least one osmotically active substance which is preferably metabolizable and preferably substantially nonionic (including zwiterionic).

A solution used in the practice of this invention is further characterized by generally having:

35 (1) sufficient total substances dissolved therein to produce an osmolarity ranging from about 260 to 5000 milliosmoles/liter (mOs), and preferably

from about 265 to 550 mOs, and more preferably from about 280 to 320 in mOs, and most preferably about 311 milliosmoles/liter.

- (2) the relationship between total (dissolved) ionic substances is such that the pH ranges from about 5 to 9, and preferably from about 6.9 to 8.6; and most preferably from about 7.35 to 7.55;
- (3) the charges of all cations equal the charges of all anions; and
- (4) the minimum total concentration of all such near equilibrium couples(s) present is at least about 0.1 millimoles per liter, and preferably is at least about 0.5 mM/l, and more preferably about 2 mM/l, while the maximum concentration thereof is preferably not more than about 465 mM/l and more preferably is not more than about 65 mM/l and most preferably is not more than about 50 mM/l.

Examples of usable osmotically active substantially nonionic substances include glucose, glycerol, fructose, sorbitol, and the like. Glucose is presently most preferred.

As hereinbelow explained, the processes and the solutions of the present invention find use in a wide variety of therapeutic applications, such as in electrolyte and fluid replacement, parenteral nutrition, and dialysis.

Various additional objects, aims, purposes, features, advantages, applications, variations and the like will be apparent to those skilled in the art from the teachings of the present specification taken with the claims.

1

DETAILED DESCRIPTION

This description is based upon best available information (including theory) known to the inventor. Any misdescription or the like, if such should exist, is not believed to alter the fundamentally correct basis and evidence supporting the present invention.

A. The Redox State

In biological cells, most reactions are catalyzed by enzymes of which an average cell may have of the order 10 of 10^4 . In one classification, enzymes may be grouped in only six functional categories.

- (1) dehydrogenases which transfer H^+ and e^- from one substrate to another by the use of cofactors, such as NAD^+ (nicotinamide adenine dinucleotide), or prosthetic groups, such as FAD (flavin adenine dinucleotide), or others;
- (2) kinases or phosphotransferases which effect the group transfer of a phosphate to a substrate usually by using a co-factor, such as ATP or other similar phosphate-containing compounds;
- (3) carbon-carbon bond group transferases which either break carbon-carbon bonds using co-factors of the co-enzyme A type or occur on a solid state substrate, such as a glycogen particle, or the surface of a fatty acid synthase multi-enzyme complex;
- (4) isomarases which effect internal rearrangements within a compound;
- (5) hydratases which either add or subtract water from a substrate; and
- (6) peptidases which break C-N bonds or create such bonds again usually taking advantage of a solid state synthetic matrix, such as a ribosome.

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1 A special class of substrates taking part of biological reactions catalyzed by enzymes are called co-factors or co-enzymes. Co-enzymes, such as, for example, NAD, become attached and detached from an enzyme during a 5 catalytic cycle, while prosthetic groups, such as flavin nucleotides or cytochromes, remain firmly attached during the catalytic cycle.

Since co-enzymes take part in multiple intra-cellular reaction within a given cellular compartment, 10 the chemical potential of the co-enzyme couple becomes of central importance in energy transformation and oxido-reductions occurring in living matter. The thermodynamic characteristics of a particular whole set of oxido-reduction reactions is dependent upon the ratio of the free 15 concentrations (strictly speaking, the activities) of the free $[NAD^+]$ and free $[NADH]$ ratio. The ratio $[NA(P)D^+]/[NAD(P)H]$, thus represents and defines the redox state, at a given pH, of a particular pyridine nucleotide couple, and this ratio then determines:

20 (1) the extent and direction of reversible reactions in near-equilibrium with that co-enzyme couple;

(2) The extent to which a co-enzyme couple can be effective as an intracellular reducing agent, 25 for example, in reducing the beta-oxpacyl co-enzyme A to beta-hydroxyacyl-coenzyme A; and

(3) the magnitude of the free-energy changes of oxido-reductions in the electron transport chain responsible for the major portion of 30 ATP synthesis.

The term "redox state" as thus used herein can be considered to refer to the oxidation-reduction state of any one or more of the three main pyridine nucleotide couples. Each of these couples are:

35 (A) The cytoplasmic $[NAD^+]/[NADH]$ linked

1 dehydrogenase reactions of: (1) Lactate dehydrogenase (EC 1.1.1.27); (2) Malate dehydrogenase (EC 1.1.1.37); and (3) Glycerol 3-phosphate Dehydrogenase (EC 1.1.1.8).

5 (B) The mitochondrial $[NAD^+]/[NADH]$ linked dehydrogenase reactions of: (1) Beta hydroxybutyrate dehydrogenase (EC 1.1.1.30); and (2) Glutamate dehydrogenase (EC 1.4.1.3).

10- (C) The cytoplasmic $[NADP^+]/[NADPH]$ linked dehydrogenase reactions of: (1) Isocitrate dehydrogenase (EC 1.1.1.42); (2) 6- Phosphogluconate dehydrogenase (EC 1.1.1.44); and (3) Malic Enzyme (EC 1.1.1.40).

15 The three pyridine nucleotide couples or pools each achieve different redox potentials because of the chemical energies of the substrates to which they are linked by their respective enzymes since the standard redox potential of $[NAD^+]/[NADH]$ is about -0.32V. Thus, the near-equilibrium NAD-linked dehydrogenases have a 20 K_{eq} of about $10^{-11} M$, the mitochondrial NAD-linked dehydrogenases have a K_{eq} of about $10^{-9} M$, and the cytoplasmic NADP linked dehydrogenases have a K_{eq} of about 1. The differences in pyridine nucleotide redox states within the cell may be considered to result from the fundamental 25 properties of matter. Over time, enzymes have evolved which take advantage of these fundamental properties to organize the chemical reactions of the cell into coherent purposeful sequences we know as metabolism.

30 The oxidation of lactate anions to pyruvate anions (that is, the loss of $2H^+$ and $2e^-$ from lactate) is accompanied by the reduction of pyridine nucleotide NAD^+ . That is, NAD^+ gains two electrons and one H^+ with the other H^+ being liberated into the aqueous media where its activity is indicated and controlled by the 35 HCO_3^-/CO_2 couple.

1 In general, the term "redox state" may also be
defined as a ratio of [oxidized substrate]/reduced sub-
strate]. The half or mid point potential Eh is convention-
ally measured as a potential in volts relative to a
5 standard hydrogen electrode potential in accordance with
the Nernst equation. The mid point potential of the NAD^+
system, that is, where the ratio of $[\text{NAD}^+]/[\text{NADH}]$ equals
1 at a pH of 7.0 and a temperature of 25 C is -0.32 volts
10 under standard conditions. The midpoint potential of
 $[\text{O}_2]/\text{H}_2\text{O}$ is +0.816 volts. The cytoplasmic pyridine
nucleotide system accepts H^+ and e^- from the organic
compounds provided to mammalian organisms and transfers
them to the mitochondrial pyridine nucleotide system where,
15 by the electron transfer system, the $2\text{H}^+ + 2\text{e}^-$ reduce
 1/2O_2 to form water while conserving the energy of the
oxidation reduction reaction by converting ADP + Pi
20 to ATP. The reaction generates energy and heat. The
redox state of cytoplasmic $[\text{NAD}^+]/[\text{NADH}]$ couple is about
-0.19 volts, that of the mitochondrial $[\text{NAD}^+]/[\text{NADH}]$
couple is about -0.28 volts while that of the cytoplasmic
25 $[\text{NADP}^+]/[\text{NADPH}]$ couple is about -0.42 volts. The last
or NADP^+ couple is a much stronger reducing agent than
the others and is used for reductive synthesis in the
body, such as the making of fatty acids from carbohydrates;
(see Krebs and Veech, 1969) in The Energy Levels and
25 Metabolic Control in Mitochondria (Papa S., Tager J.R.,
Quagliariello E. & Slater E.C. eds) pp 329-382,
Adriatica Editrice, Bari.

30 In the case of a living cell, a plurality of oxi-
dation-reduction reactions occur simultaneously. Under
normal conditions, these reactions occur in a normal
healthy cell in a predictable manner. How these various
redox states are regulated has just been described in
thermodynamic terms. The normal healthy cell keeps the
35 redox state of its free cytoplasmic $[\text{NAD}^+]/[\text{NADH}]$ redox

1 couple at a ratio of about 500 to 1500 which corresponds
to a voltage of about -0.2 volts. In this way, the cyto-
plasmic pyridine nucleotides can accept the H^+ and e^-
from the substrates or food presented to the cell so
5 that the cell may convert this food or substrate into
energy. When the cell is metabolizing very reduced sub-
strates, such as fatty acids, the cytoplasmic
[NAD⁺]/[NADH] is about 400-800. When the cell is meta-
bolizing carbohydrates or amino acids, it is obvious that
10 these compounds are already partially oxidized. There-
fore, the free cytoplasmic [NAD⁺]/[NADH] reflects the oxi-
dation level of its substrate and becomes more oxidized
in the range of about 800 to 1500.

15 The redox state of the free cytoplasmic [NAD⁺]/
[NADH] couple can be determined by various techniques,
such as by measuring the ratio of [lactate⁻]/[pyruvate⁻]
(a) in freeze clamped tissue, (b) in the venous effluent
leaving the organ in question, or (c) in the medium
bathing the tissue in question. Alternatively [L-
20 malate⁻]/[oxaloacetate⁻] or [-glycerophosphate]/
[dihydroxyacetone P] ratios in tissue may be measured,
if desired. The value of cytoplasmic [NAD⁺]/[NADH]
can then be calculated.

25 In healthy living mammals, the ratio of [L-lactate⁻]
/[pyruvate⁻] is about 6, but can range, under special
situations, such as starvation, to about 15 - 20. A
[L-lactate⁻]/[pyruvate⁻] ratio below about 20, as occurs
after ethanol consumption, because of its links to the
30 cytoplasmic [NAD⁺]/[NADH], is pathologic. A character-
istic in all cells having a low [NAD⁺]/[NADH] ratio is
believed to be demonstrable (observable) pathologic
consequences, such as tissue swelling, low
phosphorylation potential, low plasma membrane voltage,
and abnormal electrolyte distribution between intra-
35 cellular and extracellular H_2O .

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1 Similarly, the redox state of the free mito-
chondrial $[\text{NAD}^+]/[\text{NADH}]$ can be determined by various
techniques using tissues such as, for example, kidney or
liver, by measuring the ratio of [D-beta-hydroxybutyrate]
5 /[acetooacetate⁻] (a) in freeze-clamped tissue, (b) in
the venous effluent leaving such tissue, or (c) in the
fluid bathing isolated such tissues. A determination of
the free mitochondrial $[\text{NAD}^+]/[\text{NADH}]$ in other tissues,
such as brain or heart muscle, is more complex, but, in
10 some cases, can be accomplished by measurement in freeze
clamped tissue of the $[\text{alpha-keto glutarate}^-]/[\text{NH}_3^+]$ /
[glutamate⁻] ratio (see Miller A.L., Hawkins R.A., and
Veech R.L.; J. Neurochem 20, 1393-1400, 1973).

15 The normal ratio of mitochondrial $[\text{NAD}^+]/[\text{NADH}]$ is
between about 50 and 20, and the normal ratio of [beta-
hydroxybutyrate⁻]/[acetooacetate⁻] is about 1.3 to 4.
The value of mitochondrial $[\text{NAD}^+]/[\text{NADH}]$ can then be
calculated.

20 The redox state of the free cytoplasmic
 $[\text{NADP}^+]/[\text{NADPH}]$ couple is, of course, affected by the
 $[\text{CO}_2]$ of surrounding fluids. Because of the lack of
substrates which are permeable to the cell wall without
significant and variable gradients, this redox state
cannot at present be directly and totally regulated other
25 than by the intracellular metabolic links with the
cytoplasmic and mitochondrial $[\text{NAD}^+]/[\text{NADH}]$. (See Krebs
H.A. and Veech R.L.; "Pyridine Nucleotide Interrelations",
1969 in The Energy Level and Metabolic Control in
Mitochondrial in Papa S., Tager J.M., Quagliariello E.,
30 and Slater E.C., eds. pp 329-383, Adriatic Editrice,
Bari). Thus, for instance, because pyruvate reacts
in both cytoplasmic $[\text{NAD}^+]/[\text{NADH}]$ and $[\text{NADP}^+]/[\text{NADPH}]$,
administration of $[\text{HCO}_3^-]/[\text{CO}_2]$ and $[\text{L-lactate}^-]$
[pyruvate⁻] within certain narrow limits regulates these
35 ratios because:

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$$1 \quad \frac{[\text{NAD}^+]_c}{[\text{NADH}]_c} = \frac{[\text{NADP}^+]_c}{[\text{NADPH}]_c} = \frac{K_{\text{malic enzyme}} \times [\text{malate}^{2-}]}{K_{\text{LDH}} \times [\text{L-lactate}^-] [\text{CO}_2]}$$

5 Pyruvate, L-lactate and CO_2 are permeable to cell wall in a simple fashion, as are D-betahydroxybutyrate and acetoacetate, while malate²⁻ and other dicarboxylates are not.

10 While the importance of redox state to the maintenance and normalization of intracellular metabolic processes and bioenergetics has long been recognized, there has never been previously, so far as is now known, any attempt to regulate or to normalize the redox state in such mammals (including especially human patients) receiving intravenous therapy, in patients undergoing dialysis, or in patients receiving parenteral nutrition.

15 The present invention provides compositions and methods for regulating and/or normalizing the redox state in mammals (including man) treated herewith.

20 Existing electrolyte fluids make no attempt to maintain or normalize cellular redox potentials in any way whatsoever. In fact, most existing electrolyte fluids actually severely distort or make abnormal the redox balance of the cells, resulting in multiple and definable abnormalities. In this way, existing electrolyte fluids distort, such things as, for example, the rate of fat oxidation, the rate of glucose production, the rate of uric acid excretion, the rate of galactose metabolism in milk fed infants, and the like. All of these abnormalities lead to respectively, accumulation of fat in tissue, such as, for example, liver, production of either hyperglycemia or hypoglycemia, gouty crisis, cataracts, and neurological damage.

30 B. The phosphorylation Potential

35 Just as the $[\text{NAD}^+]/[\text{NADH}]$ ratio is defined as a "redox state", by analogy, it is customary to define the energy state of the adenine nucleotide co-enzyme couple

1 as the "phosphorylation potential". Because in living
 cells ATP, ADP, and HPO_4^{2-} exist in several charged forms,
 and in various complexation states with Mg^{2+} , it is
 customary to define these forms as sigma ATP, sigma ADP,
 5 and sigma Pi. The phosphorylation potential is thus
 defined by the relationship $[\text{sigma ATP}]/[\text{sigma ADP}]$
 $[\text{sigma Pi}]$.

It is clear that the reaction of oxidative phosphorylation contains both the redox state of mitochondria
 10 and the cytoplasmic phosphorylation potential. While
 the phosphorylation potential cannot apparently be controlled directly by addition of ATP and ADP to fluids
 contacting cells, since these compounds do not penetrate
 cell wall, there is, however, another reaction which is
 15 in near-equilibrium with the cytoplasmic $[\text{sigma ATP}]/$
 $[\text{sigma ADP}][\text{sigma Pi}]$ (see Veech et al. in J. Biol. Chem.
254, 6538-6547, 1979). The reaction involves the two
 most active enzymes in the glycolytic sequence found in
 nearly all living cells and catalyzed by the enzymes
 20 glyceraldehyde 3-phosphate kinase (EC 2.7.2.3).
 Veech et al. (reference just cited) provide an equation
 which defines the relationship between the free cytoplasmic
 $[\text{NAD}^+]/[\text{NADH}]$ or redox state and the cytoplasmic phosphorylation state or $[\text{sigma ATP}]/[\text{sigma ADP}][\text{sigma Pi}]$. This
 25 relationship is now and accepted by those familiar
 with this art and is (equation 5):

$$K_{G+G} = \frac{[\text{sigma 3-PG}][\text{sigma ATP}]}{[\text{sigma GAP}][\text{sigma ADP}][\text{sigma Pi}]} \cdot \frac{[\text{NADH}][\text{H}^+]}{[\text{NAD}^+]} = 1.83 \times 10^{-4}$$

or

$$K_{G+G} \cdot \frac{[\text{sigma 3-PG}]}{[\text{sigma DHAP}]/22} \cdot \frac{[\text{sigma ATP}]}{[\text{sigma ADP}][\text{sigma Pi}]} \cdot \frac{[\text{l-lactate}]}{[\text{pyruvate}]} = 1.65 \times 10^{+7} M^{-1}$$

26

1 Metabolism in any living cell may be considered to
be an ordered process whereby $[H^+]$ and electrons $[e^-]$
are removed from substrates and passed to co-enzyme ac-
ceptors which are largely cytoplasmic NAD^+ . This co-
5 factor thus has a potential in the cell for more oxidation
at about -0.19 volts than its standard potential of about
-0.32 volts so that it may accept these electrons.
The H^+ and e^- gathered in the cytoplasm, or even created
10 in the mitochondria, may then be transferred to mito-
chondria by mechanisms involving other substrates to mito-
chondrial NADH which has a lower potential of about -0.28
volts in most mammalian cells. If e^- and H^+ are produced
15 with a higher voltage, such as for example, from the oxi-
dation of succinate or fatty acids, they form reduced
FADH₂ from FAD which has a more oxidized potential and
therefore less potential energy. H^+ and electrons
produced from NADH-linked substrates produce 3 ATP for
each $1/2 O_2$ consumed while those from flavo-protein
(FAD) acceptors produce only 2. This difference in energy
20 is due to the fundamental difference in the chemical
reactions involved in producing the H^+ and e^- .

25 The fundamental process of cell respiration where
NADH is oxidized to form heat and energy is called
oxidative phosphorylation. It occurs in cellular organel-
les called mitochondria in a series of redox reactions
called the electron transport chain. The mitochondrial
electron transport system takes two electrons $[2e^-]$
from substrates and passes them up the chain to reduce
1/2 O_2 forming H_2O . The energy realized in this process
30 is conserved in the cell in a chemical form of anhydride
bond in the terminal phosphate group of adenosine tri-
phosphate (ATP). The formation of three pyrophosphate
bonds of ATP leads to the formation of H_2O and requires
3 H^+ in addition to the formation of the 1 H_2O formed from
35 NADH plus H^+ plus $2 e^-$ taken from the substrates being
oxidized by the cell. The reaction of oxidative

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1 phosphorylation is a spontaneous one (see Veech et al
in cited reference).

5 The phosphorylation potential of living cells can
be measured by determining the cellular contents of the
components of certain metabolites (see Veech R.L., In
J. Biol. Chem. 254, 6538-6547, 1979). In certain tissues,
such as brain, heart, or skeletal muscle, measurement of
the components of the creatine kinase reaction (EC 2.7.3.2)
may be used as the preceding reference describes.

10 Since on theoretical grounds Veech et al. in
J. Biol. Chem. 254, 6538-6547, 1979 showed that [creatinine]/
[creatinine-P] is in near equilibrium with the cytoplasmic
[sigma ATP]/[sigma ADP], it follows that the phosphor-
ylation potential in skeletal muscle or brain may be
evaluated in living human patients by measuring the
[sigma CRP]/[sigma Pi] ratio without resorting to freeze-
clamping of organs by the use of ³¹P NMR (nuclear-mag-
netic resonance) as has been done by Chance and others
(see Chance B., et al., Proc. Nat'l. Acad. Sci., U.S. 78
20 6714-6718, 1981). The agreement between the necessarily
destructive methods heretofore used in animals by Veech,
and the somewhat less precise but nonharmful methods of
sigma creatine-P/sigma Pi measurements with ³¹P NMR,
demonstrate that the normal value of the phosphorylation
potential or [sigma ATP]/[sigma ADP]/[sigma Pi] as esti-
mated by Veech is essentially correct (as stated above).
25 Further, the increasing availability of ³¹P NMR facilities
in academic medical centers ensures that measurements in
living human patients can be conducted without harming
them.

30 Because the cytoplasmic [sigma ATP]/[sigma ADP]
[sigma Pi] or phosphorylation potential is related to the
cytoplasmic $[NAD^+]/[NADH]$ or redox state by a near-
equilibrium reaction catalyzed by glyceraldehyde-3-
phosphate dehydrogenase and 3-phosphoglycerate kinase,

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1 it is possible to alter and regulate and normalize
the phosphorylation potential of a living cell by affecting
its redox state (as is believed to be accomplished in
the present invention).

5 If a simple, reliable chemical means were known
and/or could be devised to change the intracellular redox
state, it would of necessity have to change the other
components of the reaction which include the phosphory-
lation potential and would be of obvious fundamental
10 importance in medicine and in many other related fields
of biochemistry, physiology, molecular biology,
tissue culture, veterinary medicine, and like endeavors.
Such a chemical means is provided by the teachings of
the present invention.

15 C. Redox Active Metabolites

As above indicated, a large portion of metabolism
is devoted to energy generation which involves the re-
moval of H^+ and e^- from substrates in cytoplasm or mito-
chondria for delivery to mitochondrial electron transport
20 scheme for conversion of $2H^+$ plus $2e^-$ with $1/2 O_2$ to
yield H_2O with the liberation of about 1 volt or 54
kcal/mole of energy which is conserved in the $[sigma$
ATP] $/[\sigma ADP][\sigma Pi]$ couple. In mammalian cells,
the $[sigma ATP]/[\sigma ADP][\sigma Pi]$ has a delta G(free
25 energy in kilocalories per mole) of between -13.6 and
014.1 Kcal/mole, the transfer to this H^+ and e^- is
accomplished by a series of co-factors, the major one
being NAD (nicotinamide adenine dinucleotide) and its
phosphate (called NADP). Oxidation is defined as the
removal of electrons, and reduction as the addition of
30 electrons. The removal or addition of e^- plus H^+
from substrates is catalyzed by enzymes, the major group
of which are called dehydrogenases, as indicated above.
The enzymes (catalysts) control the rates at which reac-
35 tions occur, but the extent and the direction of a

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1 reaction, and the amount of energy (ΔG) which may
be liberated by a reaction, is determined by the inherent
energy in the chemical bonds (ΔG°) and the concentra-
tions of the reactants and products.

5 Determination of any redox or energy state must
always involve a ratio of chemical compounds, [oxidized
product]/[reduced reactant] and [oxidized co-factor]/
[reduced co-factor]. The overall reaction is thus com-
prised of two individual redox systems, one of which is
10 oxidized, while the other is reduced.

Those enzymes within a cell which are of suffi-
ciently high activity relative to the flux through the
enzyme to catalyze a state of near equilibrium are suitable
for controlling the redox state. A reaction may be ex-
15 perimentally determined to be in a state of near-
equilibrium by measuring the equilibrium constant (K_{eq})
under conditions which approximate those existing within
a cell, that is, where the ionic strength I equals 0.25,
the pH equals 7 to 7.2, the temperature equals 38°C,
20 and the free $[Mg^{2+}]$ equals 0.5 to 1mM, and also where I
equals $1/2$ sigma molarity of ions times the valence of
ions. With knowledge of the value of K_{eq} , the concentra-
tion of the reactants in a tissue may be measured in
rapidly frozen tissue. If the value of [product]/
25 [reactant] measured, in several different dehydrogenase
reactions, gives the same calculated free $[NAD(P)^{+}]$ /
[NAD(P)H] ratio, then the reaction is said to be in
"near-equilibrium" under in vivo conditions. In the case
of near-equilibrium dehydrogenase reactions, addition of
30 a predetermined amount of a ratio of product/reactant
allows one to set the $[NAD^{+}]$ / [NADH] ratio within the cell
at a predetermined level, provided the reactants penetrate
the cell wall freely or in a constant ratio one to another.
The redox state or $[NAD(P)]^{+}$ / [NAD(P)H] ratio may be set in-
35 side a cell by controlling the $[CO_2]$ and the redox state
of the cytoplasmic free $[NAD^{+}]$ / [NADH] as described pre-

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1 virously. Each of the three couples employed in this
invention is a near equilibrium couple.

2 Various cytoplasmic and mitochondrial NAD-linked
5 dehydrogenases appear to be capable of controlling or
setting the $[NAD^+]/[NADH]$ ratio in each of cytoplasm
and mitochondria. Because of the special permeability of
the complete couple of L-lactate⁻/pyruvate⁻ for cytoplasm
and D-B-hydroxybutyrate⁻/acetoacetate for mitochondria,
these two redox couples are preeminently well suited for
10 the practice of this invention. This is so because:
1) both manovalent anions in the pair distribute themselves
equally between plasma and cellular H_2O ; 2) changes in
distribution of anions between extracellular and intra-
cellular H_2O during pathological states will effect both
15 members of the couple equally through preserving the integrity
of the given redox state; 3) both couples react
with "dead end" branches off the main metabolic sequences;
4) the concentration of these normal transport metabolites
can reach very high levels in plasma of normal healthy
20 mammals under physiological conditions; and 5) the members
of both couples each contain a charge which can be
used to normalize the low $Na^+ : Cl^-$ milliequivalent
ratio characteristic of most I.V. (intravenous)
solutions.

25 The near equilibrium redox active metabolite
carboxylate couples employed in the practice of the
present invention, specifically, L-lactate⁻/pyruvate⁻
and de-betahydroxybutyrate⁻/acetoacetate⁻, constitute
safe entry points and appear to be unusual in their
30 ability to not only normalize the redox state in cyto-
plasm through the reaction of L-lactate and pyruvate
with LDH, but also to regulate the redox state in the
mitochondria through reaction of D-betahydroxybutyrate
and acetoacetate with the enzyme D-betahydroxybutyrate
35 dehydrogenase (EC 1.1.1.30) which is apparently present

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1 in most tissues at a high enough activity to maintain
near-equilibrium conditions at most times.

As indicated above (see Table 1 and related
text), previous attempts to normalize the sodium to chlor-
5 ide milliequivalent mole ratio of about 1.36 were usually
done by adding either (d,l) lactate⁻ or acetate⁻, or a
combination of lactate and acetate, or other inappropri-
ately paired carboxylate anions, leading inevitably
in all known instances to severe and measurable patholo-
10 gical consequences.

In the solutions of the present invention, one
employs at least one of the above indicated three dif-
ferent near-equilibrium couple mixtures. In each couple
mixture, the two member components are employed in a
15 definite milliequivalent ratio relative to one another.
Such a ratio is needed in order to control either the
plasma pH, or the redox state (and consequently the
phosphorylation potential), or both.

Among the possible mixture couples which could be
20 used, these three couples were selected because, for
each couple:

1. The distribution of ions between extra-
cellular fluid and intracellular fluid is
predictable in all normal and pathological
25 states.
2. It is capable of achieving and regulating a
predetermined redox state and phosphorylation
potential within most living cells.
3. At least one member thereof contains an
30 anionic charge.
4. It can be given in aqueous solution form so
that the total levels administered do not
substantially exceed total levels found under
normal physiologic conditions in mammalian
35 blood (plasma).

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1 5. Both members thereof constitute safe entry points which enter the metabolic sequence and pathways at a safe entry point and these safe entry points, are at dead end terminals in the metabolic pathways, thus avoiding any possibility of a pathologic buildup of metabolites with the consequence that a disordering of cellular metabolism would consequently result.

5 10 6. It need not induce a change in water distribution between intracellular and extracellular space.

10 7. It may be osmotically neutral in most tissues.

15 8. Administration permits control of water distribution as a result of changing redox and hence the linked phosphorylation state and the magnitude of the extracellular Na^+ Donnan forces generated thereby.

When blood levels of, respectively, l-lactate/

20 pyruvate, d-betahydroxybutyrate/acetoacetate, and bicarbonate/ CO_2 are maintained within their normal limits, then the redox state, the phosphorylation state, and the plasma pH each tend to be normalized which is achieved as a result of administration of a solution of this

25 invention.

Intracellular concentration of each member of each couple is achieved through the extracellular fluid because each of the monovalent anions chosen, namely, l-lactate and pyruvate, d-betahydroxybutyrate, and aceotacetate, and also bicarbonate, distribute themselves between plasma water, extracellular water, and intracellular water in concentration ratios or gradients which are the inverse of the hydrogen ion (concentration), thereby achieving a gradient or ratio of about 1.35 between extracellular and intracellular fluid. The nonionic

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1 dissolved CO_2 distributes itself substantially equally
between extracellular fluid and intracellular fluid.
Those learned in the art realize a redox state must
be defined at a certain pH, or $[\text{H}^+]$ ion concentration.
5 The near-equilibrium couple $[\text{HCO}_3^-]/[\text{CO}_2]$ defines the cel-
lular pH or $[\text{H}^+]$ concentration. This near-
equilibrium couple is therefore an integral part of the
redox state. Preferably the level of sigma $[\text{HCO}_3^-]$
plus $[\text{CO}_2]$ present in any given solution of this invention
10 may vary under normal physiological conditions from about
10mM/l to 40mM/l, but in general, is (when present) in
the range from about 25 to 35 mM/l. The milliequivalent
ratio of $[\text{HCO}_3]/[\text{CO}_2]$, of course, in effect, is defined
so as to give a $[\text{H}^+]$ ion concentration, or pH, in the
15 physiological range as defined above.

The redox and phosphorylation states in various
tissues in the rat have been given by Veech et al. J.
Biol. Chem. 254, 6538-6547, 1979 and for the redox states
in Veech, Eggleston and Krebs, Biochem. J. 115, 609-
20 619, 1969. The same general principles are believed to
hold for man, but cannot be directly proved since freeze
clamping is not possible. MNR measured estimates of the
phosphorylation potential in brain and muscle in living
humans, however, agree well with these figures derived
25 by freeze clamping procedures.

By the term "plasma" or "blood plasma" as used
herein conventional general reference is had to the liquid
part of the blood as distinguished from the corpuscles.
Plasma can be prepared by various techniques well known
30 to those familiar with this art typically using centri-
fugal force to separate a supernatant (which is plasma)
after non-coagulated blood is centrifuged.

1 By the term "extracellular fluid" as used herein
conventional general reference is had to all body fluids
in extracellular spaces outside of the circulatory system
(e.g. the blood) and outside of intracellular fluid in
5 a mammal (typically constituting about 15% of the weight
of a mammal).

10 By the term "intracellular fluid" as used herein
conventional general reference is had to the fluid within
cells which constitutes about 57% of total mammalian
body weight.

15 It is well known that (see Black DAK. Lancet i
305-12 1953) infusions into a mammal of large amounts
sodium and chloride in a solution milliequivalent ratio
of 1 to 1 lead inherently to hyperchlloremic acidosis.
20 This knowledge lead to the development of such well known
solutions as lactated Ringers, and also to the composi-
tions used in most dialysis solutions, wherein, in a
majority of cases, the sodium to chloride milli-
equivalent ratio is normalized compared to plasma values
25 by the addition of various organic anions (as described
above). These organic anions chosen in the prior art
are as described above. In no known prior art case,
however, were any solutions with a normalized Na:Cl
milliequivalent ratio produced which did not use organic
ions in such a way as to inherently lead to severe and
measurable metabolic abnormalities and pathologic
consequences. Mixtures of redox pairs nor $\text{HCO}_3^-/\text{CO}_2$
30 were not generally used to normalize the $\text{Na}^+:\text{Cl}^-$ ratio
nor were the reasons known why a choice of near equili-
brium matched couples was desirable. Correction of this
ratio between sodium cation and chloride anion by the
mixture couples as taught by the present invention
eliminates the pathologic consequences of all the
prior art electrolyte solution compositions. In addi-
35 tion, the solution compositions of this invention tend

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1 to normalize plasma inorganic electrolyte composition and
to correct the anion gap which in many instances could
not be accomplished by prior art electrolyte solutions.

5 Thus, in summary, the compositions of this invention
tend to normalize (a) plasma pH, (b) composition of
major plasma inorganic electrolytes, (including the
milliequivalent ratio of $\text{Na}^+ \text{Cl}^-$ and the anion gap),
(c) the redox state, and (d) the phosphorylation potential.
10 These normalizations are obtained and achieved
without the abnormal, pathological consequences
inherent in all known prior art solutions. No other
man-made solutions are presently known which will ac-
complish this combination of results.

D. Other Possible Benefits (Theorized).

15 It is theorized, and there is no intent to be
bound by theory herein, that the solutions of the
present invention, in addition to the properties above
described, further tend to normalize at least one
of the following states:

20 1. Distribution of water between intracellular
and extracellular compartments,
2. Distribution of major inorganic electrolytes
between intracellular and extracellular fluid,
3. Transmembrane cellular potential, and
25 4. The degree of organization within the living
cell or its entropy.

30 The ratio of the chemical activity of free water
on each side of a typical normal mammalian cell membrane
is always unity. Movement of water across such a cell
membrane is achieved by the movement of osmotically
active substances. Changing the cellular phosphorylation
potential, through the NaK ATPase, therefore,

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1 Transmembrane cellular potential can be measured
 by known (e.g. conventional) techniques: such as with
 electrodes or probes, and the like. Calculation of such
 cellular voltage can be achieved from a measurement of
 5 the distribution of chloride ions between intracellular
 and extracellular fluid following Nernst's law.

10 A quantitative relationship is theorized to exist
 involving redox state, phosphorylation potential and
 the above referenced three states. This relationship
 may be expressed by the following equation:

(7.)

$$\Delta G = 0 = \Delta G^{\circ}_{ATPase} + \Delta G^{\circ} \frac{[Na^+]}{[Na^+]_i} \dots + RT \ln \frac{[\epsilon ADP][\epsilon P_i]}{[\epsilon ATP]} \\ 15 + RT \ln \frac{[Na^+]_o^3 [K^+]_i^2 [Cl^-]_o}{[Na^+]_i^3 [K^+]_o^2 [Cl^-]_i} + T \Delta S$$

wherein

20 The values of the various terms in the foregoing
 equation of are given as follows (for muscle and brain):
 (7.1)

$$\Delta G = 0 - -7.73 \text{ kcal/mol} + 0 = (-6.3 \text{ kcal/mol}) \\ + 8.4 \text{ kcal/mol} + 5.6 \text{ kcal/mol}$$

25 In the foregoing equation, the phosphorylation
 potential is shown to be in a state of near equilibrium
 with the substrates of the sodium potassium ATPase.
 Since the chloride ion is cell wall permeable, this ion
 distributes itself in conformity with the transmembrane
 cellular potential. Movement of three sodium ions out
 30 of the cell and two potassium ions into the cell across
 the cell membrane necessarily results, from the law of
 electrical neutrality, in the movement of one chloride
 ion from inside the cell to outside the cell across
 the cell membrane. This makes the sodium potassium
 35 ATPase, in effect, an osmopump resulting in the export

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1 of two milliosmoles per ATP hydrolyzed. This pump
is electro-neutral.

5 The T delta S term, which is approximately
5.6 kilocalories per mole of ATP hydrolyzed, is an
entropy term. It, therefore, refers the state of
randomness within the cell. The positive nature of this
10 entropy term indicates that a high degree of order is
imposed on the intracellular environment. In terms of
quantum and statistical mechanics, the number of ways
of achieving a certain energy state is called its de-
generacy (Ω). The Boltzmann equation defines S (or
15 entropy) as $S = K_B \ln \Omega$, where Boltzmann's constant
(which relates the gas constant to Avogadro's number),
or $K_B = 1.38 \times 10^{-23} \text{ J}/\text{K}$.

15 It follows from the foregoing equation 7, above,
that the distribution of calcium inside the cell is a
function of the cube of the respective sodium concentra-
tions inside and outside of the cell because of the action
of the high-activity sodium-calcium exchange enzyme.

20 The following equation shows the relationship:

$$K_{\text{Na/Ca}} = \frac{[\text{Na}^+]_i^3 [\text{Ca}^{2+}]_o [\text{Cl}^-]_i}{[\text{Na}^+]_o^3 [\text{Ca}^{2+}]_i [\text{Cl}^-]_o}$$

where:

25 $[\text{ }]_i$ ~ intracellular concentration in cytoplasmic H_2O

$[\text{ }]_o$ ~ concentration in extracellular H_2O .

Unlike the simple NaK ATPase which moves 2
mOsmoles out of the cell thus moving H_2O with it, the
result of moving Ca^{2+} out of the cell by the Na-Ca
30 exchanger is to move a net of 3 mOsmoles into the cell,
thus increasing the cells water content. The NaK
ATPase must then operate again to move the excess
sodium out in exchange for K^+ to restore osmotic
equilibrium between extracellular space H_2O and cell
35 H_2O .

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1 The net result of the foregoing equation (7)
 is that the water of both intracellular and extracellular fluid is a function of the sodium/potassium ATPase
 (EC 3.6.1.3) and also of the phosphorylation
 5 potential.

It can be empirically seen that the voltage across a cell membrane is inversely related to the chloride distribution and the phosphorylation potential.

10 Correlation between phosphorylation potential, intracellular chloride and transmembrane cellular potential for various mammalian tissues is illustrated by Table II below:

Table IIa

15 Correlation between Phosphorylation Potential, Intracellular Chloride and Transmembrane Cellular Potential.

	$[\Sigma \text{ATP}]$	$[\text{Cl}^-]_i$	ΔE
	$[\Sigma \text{ADP}] [\Sigma \text{Pi}]$	mEq/l	mV
20	M^{-1}		
red cell	7,000	90	- 9
liver	15,000	40	-40
brain or muscle	30,000	7-9	-70

From Table II, it is seen that low phosphorylation potential correlates with a high intracellular chloride, and a low transmembrane cellular potential correlates with the inherent setting of the potential as a function of the Donnan-active material within the cell with the phosphorylation potential merely overcoming the Donnan forces so as to export two milliosmoles, as described in equation 7.

Because of the voltage dependent permeant nature of chloride ion to most non-epithelial tissues (Ho, MK, Guidotti G. J. Biol Chem 250: 675-683, 1975) the induction of high extra cellular chloride, such

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1 as occurs, for example, in current intravenous electro-
lyte therapy, must have profound pathological conse-
quences for the metabolism of the cell, even though the
purpose of such intravenous and dialysis therapy is to
5 normalize the water and electrolyte concentrations of
the various mammalian body cellular compartments.

This is so because the ratio

$$\frac{[Na^+]_o^3 [K^+]_i^2 [Cl^-]_o}{[Na^+]_i^3 [K^+]_o^2 [Cl^-]_i}$$

10 and the $T\Delta S$ term link the cellular phosphorylation and
the cellular redox states to intracellular and extra-
cellular water and the electrolyte concentrations of
 Na^+ , K^+ , Cl^- and also Ca^{2+} .

E. Electrolyte Solution Preparation

15 The electrolyte solutions of the present invention
can be prepared by any convenient or conventional pro-
cedure.

As a matter of accuracy, the compositions of
this invention can be described in terms of their ion
20 contents which can be expressed either in terms of milli-
moles per liter of solution, or milliequivalents per
liter of solution. It is standard practice in this art
in describing a given solution to separate anions from
cations, and nonionics from ionic materials; this
25 practice is followed herein in the main. As those skilled
in the art will readily appreciate, a translation or
conversion of millimoles per liter of solution, or of
milliequivalents per liter of solution, into grams of
a given salt added per liter of water is routine and
30 is given in any standard text book in the field, such
as, for example, "Data For Biochemical Research"
(1969) (Dawson R.M.C., Elliott W.H., Jones K.M., Eds.).
Clarendon Press, Oxford at pages 507 and 508. This
reference illustrates not only the salt starting
35 materials, but also the order of addition of same

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1 in the preparation of certain illustrative prior art
electrolyte solutions shown therein. Solutions of this
invention are readily prepared by this type of procedure.
The particular salt combination used for a given solution
5 may change from time to time in a manufacturing operation
as those skilled in the art well know. The significant
factor is that the final concentrations of respective
component ions in any given solution remain as speci-
fied or desired. In view of the developed state of this
10 art, no detailed description of electrolyte solution
preparation procedures is believed to be necessary or
desirable herein.

The solutions of this invention, and the component
materials incorporated thereinto, are, in general,
15 formulated, so as to contain a combination of a the
desired physiological $\text{Na}^+:\text{Cl}^-$ milliequivalent ratio
normality, one or more of these three near-equilibrium
couple(s), and other components.

Thus, various initially existing pathological
20 conditions can be ameliorated by practice of the processes
and the compositions of the present invention, depending
upon the particular solution used and the particular
use conditions and circumstances in any given use situa-
tion. Thus, by this practice of this invention, one
25 can accomplish in a physiologically acceptable manner
the removable of metabolic products from cellular water,
the replacement of body fluids and electrolytes, and
the administration of nutrients, and the like, as desired.
The solutions may be administered in any fashion desired
30 so long as they contact living mammalian tissue.
Administration can be accomplished by any convenient
technique, such as for examples, intravenously, intra-
arterially, intradermally, intrathecally, orally
(especially when the solution con . ins the non-
35 bicarbonate containing couples),

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1 across a semi-permeable membrane, or the like, as those
skilled in the art will readily appreciate. The solu-
tions of this invention as prepared are, in general,
well suited for the administration of therapeutic agents
5 to living mammals.

When bicarbonate anions are not present, then the
level of combined (or sigma) l-lactate/pyruvate and/or
d-betahydroxybutyrate/acetoacetate present in a solution
of this invention is optionally greater than when bi-
10 carbonate is present in order to achieve the desired
milliequivalent ratio of sodium to chloride, as indi-
cated. The concentration of either sigma l-lactate/
pyruvate and/or of d-betahydroxybutyrate/acetoacetate
15 in a given solution of this invention can thus range up
to the full maximum quantity desired (within the limits
described herein). It is presently preferred, particu-
larly when no bicarbonate is present, to employ a
mixture of l-lactate/pyruvate with a mixture of d-
betahydroxybutyrate/acetoacetate.

20 Those skilled in the art will realize that in
any given solution of this invention one can incorporate
an excess of one or more individual members of any one
mixture couple of this invention so that (a) the ratio
of one member to the other of any given couple and (b)
25 the total quantity of both mixtures or members lies
outside of the ranges hereinabove described without
departing from the spirit or scope of the invention.
Such a single member excess is not recommended when
practicing the present invention. However, if such a
30 single member excess does occur, the amount of the
excess can be calculated by determining the maximum
ratio of one couple member to the other which can
be present in accord with the above teachings, and then
the quantity of one couple member remaining (or present)
35 which is outside of this ratio range may be considered
to constitute an excess. The effect of such an excess

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1 is evidently merely to cut down, but not to eliminate,
the efficacy of what effect would otherwise be obtained
by using only a solution which contains mole ratios and
quantities of respective mixture couples within the
5 spirit and scope teachings of this invention.

In the making of solutions of this invention,
it is preferred to employ the optically active l-lactate
salts or l-lactic acid (which will make the desired l-
lactate anions in solution), and also similarly to employ
10 d-betahydroxybutyric acid or d-betahydroxybutyrate salts
(which will make the desired d-betahydroxybutyrate anions
in solution). Choice of particular salt or acid (or
mixture) used in any given case depends among various
15 factors, such as upon the other starting inorganic salts
which a formulator desires to use (based upon availability,
cost, and like factors), all as will be readily
appreciated by those skilled in the art. Racemic (d-l)
mixtures could be used, but their use is preferably
20 avoided since these unnatural isomers are known to be
associated with specific toxic effects. Racemates can
be metabolized. If such are used, the ratios of one
member to another in the respective near equilibrium
25 couples involved should be based upon the quantity of
particular optically active form present (e.g. either
[l-lactate⁻] or [d-betahydroxybutyrate⁻]), as the case
may be.

In the solutions of this invention at the pH
ranges described, not all couple member material of any
given couple will be in an ionized (anionic or disso-
30 ciated) form; a portion of this material will be in an
un-ionized (undissociated) form. Typically, the quantity
of undissociated material (such as l-lactate acid,
pyruvic acid, d-betahydroxybutyric acid, acetoacetic,
35 sodium bicarbonate, carbonic acid, or the like) is
not more than about 0.1% of the total quantity of all

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1 material of any given species (e.g. l-lactate, pyruvate,
d-betahydroxybutyrate, acetoacetate, or bicarbonate).
5 For purposes of calculating a milliequivalent ratio,
molar concentration, or the like, it is preferred to
base computations upon the total material of any given
species which is present in a solution of this
invention.

10 The carbon dioxide, when used, can be introduced either as a gas, preferably using conventional aeration apparatus to effect a solubilization of CO_2 in a solution, or it can be generated in situ from a dissolved metal (such as sodium (preferred), potassium, calcium or magnesium) salt of bicarbonate in combination with a dissolved acid (lactic, pyruvic, betahydroxybutyric, or acetoacetic) in respective proportions of each such that the total quantity of dissolved carbon dioxide so generated is within the ranges described herein for use in a solution of this invention.

15 As elsewhere indicated herein, if desired, a solution of this invention can also contain various known additives in concentrations taught by this art, but it is presently preferred not to employ anions and non-ionics which will not be safe entry points.

20 In general, a solution of this invention should contain as a minimum a total of sigma (lactate/pyruvate and/or sigma betahydroxybutyrate/acetoacetate) and/or sigma bicarbonate/carbon dioxide which is at least about 0.5 millimoles per liter as indicated. Below these levels, benefits in normalization of body 25 metabolism as explained above are apparently achievable, but such benefits become increasingly difficult to demonstrate and prove by state of the art techniques of measurement. Consequently, it is preferred to avoid, 30 if possible, homeopathic possibilities by using minimum 35 concentrations as above indicated.

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1 When bicarbonate is present, the total quantity
of sigma (lactate/pyruvate and/or betahydroxybutyrate/
acetoacetate) used can generally be reduced which is
now believed to be desirable. Thus, when bicarbonate
5 is present, the total sigma (l-lactate/pyruvate and/or
d-betahydroxybutyrate/acetoacetate) is preferably about
2 to 17 millimoles per liter.

When a solution of this invention contains
at least one osmotically active substance (preferably
10 metabolizable and nonionic), it is added to provide
nutritional or osmotic requirements. Since it is
uncharged, it does not therefore contribute to normalizing
the $\text{Na}^+:\text{Cl}^-$ ratio or to correcting the anion gap.

F. Classification and Usage of Electrolyte Solutions

15 All of the formulations of this invention
from a composition viewpoint fall into what can be
regarded generally as being either one of two distinct
classes:

20 Class I which comprises fluids containing
at least one and not more than two metallic
cations selected from the group consisting
of sodium, potassium, calcium and magnesium,
while

25 Class II which comprises solutions
containing at least three and typically
not more than four metallic cations
selected from the same group.

30 Class I fluids are typically administered at
dose levels which are not greater than about 1 liter
per human adult patient per 24 hour day, one typical
dose level being 500 ml per such patient per 24
hour day.

35 Class II fluids are typically administered at
dose levels chosen by the physician, and these levels
can range from 0 to greater than 100 liters per human

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1 adult patient per 24 hour day, depending upon
circumstances.

5 Each of the inorganic electrolytes present in
a solution of this invention is typically present in
an amount of at least about 0.5 mM/l thus clearly qual-
ifying them as "electrolytes" as such rather than as
trace metals, such as is associated with levels of
iron, manganese, zinc and the like in normal plasma
and which trace metals can be present in normal plasma
10 at levels less than about 0.4 mM/l. If desired, of
course, trace materials can be added to solutions of
this invention.

15 Each of the cations sodium, potassium, calcium,
and magnesium and each of the anions bicarbonate, chlor-
ide, and phosphate are normally found in the plasma
and tissue of mammals at concentration levels greater
than or equal to about 1 millimolar per liter of body
fluid (see Table I). The solutions of this invention,
in general, contain respective inorganic electrolyte
20 concentrations which resemble the corresponding concen-
trations of such electrolytes in plasma (when any one
of such electrolytes is present in any given solution
of this invention).

25 Class I solutions are useful as intravenous solu-
tions for electrolyte and fluid therapy especially where
no more than about 10% of total blood volume (about
500 ml in an adult human) is to be administered over
a 24 hour day. Solutions of this type have been used
in the treatment of hemorrhagic shock where 2400
30 mOsmolar NaCl solutions have been advocated. (See
Velosco IT, Pontieri V, Rocha M, Silva E,
Lopes OU. Am J Physiol 239: H664-673, 1980).

35 Class II solutions find use in intra-
venous applications where over 10% of total blood
volume (about 500 ml in an adult human) is needed to

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1 to be given to a human adult over a 24 hour day.
Administration can be made, for example, to a normal
5 human with an impairment or injury, such as loss of
limb or the like, or to a human with impaired renal
excretion: Class II solutions can be used as an
improvement for lactated Ringer's solution.

10 Class II solutions also are useful in dialysis,
peritoneal, ambulatory peritoneal dialysis or hemo-
dialysis, where perhaps 120-160 liters per hemodialysis
improve existing acetate or lactate containing solu-
tions, but use of acetate is not desired in the prac-
tice of this invention.

15 Given the solutions of this invention, a physician
may henceforth wish to administer normal or hypertonic
saline solution only to correct a condition of metabolic
alkalosis since giving $\text{Na}^+:\text{Cl}^-$ in a 1:1 milliequivalent
ratio causes acidosis and other disturbances recognized
herein. The solutions described herein improve normal
20 saline solution.

25 Solutions of Class II can be used as such, or
can be employed as diluent for plasma extenders or for
reconstituted frozen blood. For example, dehydrated
plasma can be dissolved and dispersed in a solution of
Class II so as to produce an injectable solution, as
those familiar with the art will appreciate.

30 Each one of these Class I and II solutions can
be considered to be characteristically comprised of
four subgroups which can be stated briefly as
follows:

A. Solutions containing only inorganic ions
and one or more of our near-equilibrium
couples of organic anions pairs with
which chloride anions are included.

1 B. Solutions containing in addition to such inorganic ions and organic ion pairs a mixture of bicarbonate and carbon dioxide.

5 C. Solutions containing such inorganic ions and organic ion pairs plus non ionic materials.

10 D. Solutions containing in addition to the inorganic ionic material both mixtures of bicarbonate and carbon dioxide (as characterized in B above) plus other nonionics (of the type characterized in C above).

As indicated above, avoidance of substances in solutions of this invention which do not constitute safe entry points is preferred. For example, use of such nonionic osmotically active substances as fructose and glycerol are preferably avoided and are not recommended for use in the practice of this invention. Also, avoidance of the organic anions used in the prior art which are not safe entry points is recommended, including use of lactate alone, acetate alone, lactate and acetate together, gluconate, citrate, and the like.

Prior art in dialysis fluids show that the composition of the fluids now commercially used evidently is intended to approximate that of plasma with the proviso that the anion gap is typically corrected with abnormal amounts of typically acetate or lactate. The suggestion has also been made in the prior art dialysis fluid composition should approximate the composition of interstitial (extracellular) fluid. While such compositional approximations now appear to be essentially incorrect especially from the standpoint of achieving dialysis fluids of maximal safety and utility and patient benefit, it is submitted that such approximations can be substantially

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1 benefitted by compounding dialysis solutions in accord
with the teachings of the present invention (both for
hemo- and peritoneal dialysis).

5 Solution compositions of the present invention
of Class I and Class II are generically characterized
herein above. The following Table III summarizes
preferred solutions of this invention in terms of compo-
sition at the time of administration (e.g., water
having dissolved therein each of the indicated components
10 in the respective amounts indicated).

15 With regard to the term "nonionics" in a
solution or process of this invention, those skilled
in the art will appreciate that this term connotes no
net charge on the molecule involved at the particular
solution pH specified.

20 Solutions of this invention can be prepared
as concentrates which at 0.8 molar solutes or greater
will inhibit bacterial growth, as those skilled in the
art will appreciate, and such concentrates can then
be diluted with water before administration to prepare
compositions of this invention.

25 In general, solutions of this invention are
believed to be preparable so as to be storage stable
for periods of time at least sufficient to permit pack-
aging, intermediate storage in sealed containers,
followed by administered.

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Table III
Generic Compositions of Class I and Class II Solutions

5	Component	Composition of time of Administration Quantity Range (millimoles per liter)	
		broad	preferred
	Total cations (mEq/L)	1 to about 2400	130 to 170
10	(1) sodium ⁺	1 to about 2400	130 to 165
	(2) potassium ⁺	0 to about 90	0 to 5
	(3) calcium ⁺⁺	0 to about 60	0 to 1.5
	(4) magnesium ⁺⁺	0 to about 15	0 to 1
	Total anions (mEq/L)	about 1 to 2400	130 to 170
15	(5) chloride ⁻	0.6 to about 1940	80 to 130
	(6) bicarbonate ⁻	0 to about 465	0 to 60
	(7) sigma l-lactate ⁻ / plus pyruvate	0 to about 465	0 to 60
	(8) sigma d-betahydroxy- butyrate/plus acetooacetate ⁻	0 to about 465	0 to 60
20	(9) sigma (6+7+8)	0.1 to about 465	25 to 65
	Total nonionics	0 to about 2400	0 to 305
	(10) carbon dioxide	0 to about 25	1 to 5
	(11) osmotically active substances*	0 to about 2400	0 to 300

In Table III solutions the component interrelationships are always such that the following holds:

30	(12) mEq.ratio of bicarbonate ⁻ / CO ₂	about 0.1/1 to 55/0.1	0.1 to 55/0.1
	(13) mEq.ration of l-lactate / pyruvate	about 20/1 to 1/1	10/1 to 5/1
35	(14) mEq.ratio of d-betahydroxybutyrate ⁻ / acetooacetate	about 6/1 to 0.5/1	3/1 to 1.5/1

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(15) mEq.ratio of Na:Cl	about 1.24 to 1.60	1.24 to 1.6
(16) Osmolarity of Solution	about 260 to 5000	280 to 545
(17) pH of Solutions	about 5 to 9	5 to 9
5 * Glucose preferred		

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Optionally, solutions of this invention as shown in Table III can additionally contain:

5 (a) from 0 to about 25 millimoles per liter of sigma inorganic phosphate (e.g. all inorganic phosphate, including mono-, di-, and tri-
10 valent phosphate ions), and
(b) from 0 to about 2 millimoles per liter of sigma inorganic sulfate (e.g. all inorganic sulfate including non ionized dissolved salts).

10 The electrolyte solutions of such Table III, as indicated above, are useful in such applications as intravenous administration for replacement of electrolytes and fluids, for parenteral nutrition, for dialysis, and the like. For a particular field of use and/or end 15 use applications, the formulation of any given solution can be optimized in accord with the desires of the formulator. Thus, in general, the present invention provides one aspect an in vivo process which

20 (a) tends to maintain a normal plasma milliequivalent ratio of sodium cations to chloride anions,
(b) tends to maintain normal plasma and cellular pH, and
(c) tends to maintain normal cellular cofactor 25 ratios (that is, tends to maintain and regulate a normal cellular redox state and a normal cellular phosphorylation potential).

30 This process is practiced by introducing into a living mammal a physiologically effective amount of an aqueous solution as above characterized. Introducing can be accomplished by any known procedure as herein indicated. The physiologically effective amounts are as herein indicated.

35 Class I solutions which are particularly suited for electrolyte and fluid therapy are subgenerically characterized in Table IV below. Each Table IV solution

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comprises water which has dissolved therein each of the indicated components in the respective amount indicated. In this Table IV the "preferred" class of embodiments (so identified) can be regarded as being usable either 5 as such, or as concentrates which can be further diluted so long as nonionic material is included to keep the final osmolarity above about 260/mOsmoles/L. In the latter case, the diluted solutions should contain added dissolved nonionic material (preferably glucose) with 10 care being taken to preserve in the product diluted solution the various ratios, osmolarity and pH values, all as shown in such Table IV.

Such Class I solutions are used, in accord with this invention, in an in vivo process for accomplishing 15 electrolyte and fluid therapy in a mammal. This process:

- (a) tends to maintain a normal plasma milliequivalent ratio of sodium cations to chloride anions,
- (b) tends to maintain normal plasma and 20 cellular pH, and
- (c) tends to maintain normal cellular cofactor ratios.

This process comprises introducing intravenously 25 into a mammal at a physiologically effective rate a quantity of such a solution in an amount which is not more than about 1 liter per 70 kilograms of mammal body weight per 24 hour day.

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Table IV

Class I Solutions Particularly Suited for Electrolyte and Fluid Therapy

Composition at time of
Administration

5

Quantity Range

(millimoles per liter)

Component	broad	preferred
Total cations (mEq/L)	1 to about 2400	130 to 170
(1) sodium ⁺	1 to about 2400	130 to 165
(2) potassium ⁺	0 to about 90	0 to 10
(3) calcium ⁺⁺	0 to about 60	0 to 5
(4) magnesium ⁺⁺	0 to about 15	0 to 3
Total anions (mEq/L)	1 to about 2400	130 to 170
(5) chloride ⁻	0.6 to about 1935	80 to 130
(6) bicarbonate ⁻	0 to about 465	0 to 60
(7) sigma l-lactate/ plus pyruvate	0 to about 465	0 to 60
(8) sigma d-betahydroxy-		
20 butyrate plus acetoacetate	0 to about 465	0 to 60
(9) sigma (6+7+8)	0.4 to about 465	25 to 60
Total nonionics	0 to about 2400	0 to 300
(10) carbon dioxide	0 to about 25	0 to 5
25 (11) osmotically active substances*	0 to about 2400	0 to 300

In Table IV solutions, the component interrelationships are always such that:

30 (12) mEq.ratio of

$$\frac{\text{HCO}_3}{\text{CO}_2} \text{ about } 0.1/1 \text{ to } 55/0.1 \quad 12/1 \text{ to } 85/1$$

35 (13) mEq.ratio of

$$\text{l-lactate} / \text{pyruvate} \quad \text{about } 20/1 \text{ to } 1/1 \quad 10/1 \text{ to } 5/1$$

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(14) mEq.ratio of d- betahydroxybutyrate / acetoacetate	about 6/1 to 0.5/1	3/1 to 1.5/1
(15) mEq.ratio of Na:CL	about 1.24 to 1.6	1.26 to 1.6
5. (16) Milliosmolarity of Solution	about 260 to 5000	260 to 540
(17) pH of solution *glucose preferred	about 5 to 9	7 to 8

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Class II solutions which are particularly suited for electrolyte and fluid therapy are sub-
5 generically characterized in Table V below. As before, each Table V solution comprises water which has dissolved therein the indicated components in the
10 respective amount indicated. In this Table V, the "preferred" class of embodiments (so identified) can be regarded as being representative of compositions which are now believed to be suitable for usage, for example, by hospitals and the like. In making and using all
15 these solutions, care should be taken to preserve the various ratios, osmolarity, and pH values, all as shown in such Table V.

Such Class II solutions are used, in accord with this invention in an in vivo process for
15 accomplishing electrolyte and fluid therapy in a mammal. Parenteral nutrition optionally can be concurrently accomplished (depending upon the content of nutrients, such as nonionic osmotically active substances (like
20 glucose, or other conventional additives, including amino acids). As with the process involving Class I solutions, this process:

- (a) tends to maintain the normal plasma milliequivalent ratio of sodium cations to chloride anions, and
- (b) tends to maintain normal plasma and cellular pH ratios, and
- (c) tends to maintain normal cofactor ratios.

This process comprises intravascularly introducing into
25 the blood of a mammal a physiologically effective amount of such a solution. The quantity introduced can vary per 24 hour day per patient depending upon the circumstances, patient condition, physicians purpose, and the like. No minimum or maximum definite limit on
30 safe usage quantity is now known or believed to exist.

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Table V
Generic Composition of Class II Solutions for Electrolyte and
Fluid Therapy

5	Component	Composition at time of Administration	
		Quantity Range (millimoles per liter)	
		broad	preferred
	Total cations (mEq/L)	1 to about 170	136 to 170
10	(1) sodium ⁺	1 to about 170	130 to 160
	(2) potassium ⁺	0 to about 10	3 to 5
	(3) calcium ⁺⁺	0 to about 5	1 to 1.5
	(4) magnesium ⁺⁺	0 to about 5	0.5 to 1.0
	Total anions	1 to about 170	136 to 170
15	(5) chloride ⁻	0.6 to about 137	81 to 129
	(6) bicarbonate ⁻	0 to about 64	0 to 51
	(7) sigma l-lactate ⁻ / and pyruvate	0 to about 64	0 to 51
	(8) sigma d-betahydroxy- butyrate /and acetoacetate	0 to about 64	0 to 51
	(9) sigma (6+7+8)	0.4 to about 64	25 to 51
	Total nonionics	about 0 to 625	0 to 305
	(10) carbon dioxide	about 0 to 25	0 to 5
25	(11) osmotically active substances*	about 0 to 600	0 to 300

In Table V solutions the component interrelationships are always such that:

30	(12) mEq.ratio of HCO_3^- / CO_2	about 0.1/1 to 55/0.1	0.1/1 to 55/0.1
	(13) mEq.ratio of l-lactate ⁻ / pyruvate	about 20/1 to 1/1	10/1 to 5/1
	(14) mEq.ratio of d-betahydroxybutyrate ⁻ / acetoacetate	about 6/1 to 0.5/1	3/1 to 1.5/1
35	(15) mEq.ratio of Na:Cl	about 1.24 to 1.6	1.24 to 1.6

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(16) Milliosmolarity of Solution	about 260 to 950	260 to 550
(17) pH of Solution	about 5 to 9	5 to 9
*glucose preferred		

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Class II solutions which are particularly suited for use in dialysis (whether hemo- or peritoneal) are subgenerically characterized in Table IV below.

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Table VI
Class II Solutions Particularly Suited for Dialysis
(Hemo- & Peritoneal)

5	Component	Composition at Time of Administration	
		Quantity Range (millimoles per liter)	
		broad	preferred
	Total cations (mEq/L)	about 130 to 170	136 to 155
10	(1) sodium ⁺	about 130 to 155	135 to 145
	(2) potassium ⁺	0 to about 5	0 to 4
	(3) calcium ⁺⁺	0 to about 3	0 to 1.7
	(4) magnesium ⁺⁺	0 to about 2	0.3 to 1
	Total anions (mEq/L)	about 130 to 170	136 to 155
15	(5) chloride ⁻	about 81 to 125	86 to 104
	(6) bicarbonate ⁻	0 to about 60	25 to 45
	(7) sigma l-lactate ⁻ /plus pyruvate	0 to about 60	2 to 10
	(8) sigma d-betahydroxybutyrate ⁻ / plus acetooacetate	0 to about 60	1 to 5
20	(9) sum (6+7+8)	about 25 to 60	27 to 55
	Total nonionics	0 to about 525	11 to 280
	(10) carbon dioxide	0 to about 25	0.5 to 2
	(11) osmotically active substance*	0 to about 500	10 to 280
25	In Table VI Solutions, the component interrelationships are always such that:		
	(12) mEq. ratio HCO_3^- / CO_2	about 0.1/1 to 55/0.1	19/1 to 8/1
30	(13) mEq. ratio of l-lactate ⁻ / pyruvate	about 20/1 to 1/1	10/1 to 5/1
	(14) mEq. ratio of Na:Cl	about 1.24 to 1.6	1.36 to 1.5
	(16) Milliosmolarity of Solution	about 260 to 850	280 to 320
35	(17) pH of Solutions *glucose preferred	about 5 to 9	7.35 to 8

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Class II solutions which are within the scope of Table VI above and which are particularly suited for hemodialysis are subgenerically characterized in Table VII below. As before, each Table VII solution comprises 5 water which as dissolved therein the indicated components in the respective amounts indicated.

Such Class II solutions in Table VII are suitable for use in a hemodialysis process of the generally known and conventional type where renal function 10 of a living mammal is replaced in whole or in part by dialysis. In hemodialysis, portions of the blood of such mammal are continuously passed over one face of a dialysis membrane (which is incorporated preferably a high surface area cartridge-like structure) while the 15 opposed face of such membrane is contacted with a dialysis fluid, thereby to achieve a change in the chemical composition of the body fluids after the so dialyzed blood is returned to the mammal's vascular system. Duration of a conventional hemodialysis can vary, 20 depending upon equipment, conditions, patient condition, and the like, but typically can extend for a time of from about 3 to 5 hours. Optionally, but preferably, the dialysis membrane used in combination with the associated apparatus is such that the blood so passed 25 over such membrane can be pressurized during such passage (typically and conventionally up to about 300 grams per cubic centimeter), thereby to produce what is known in the dialysis art as "ultrafiltration". In the conventional hemodialysis procedure, the dialysis fluid 30 is an aqueous solution which contains dissolved therein the same principal inorganic electrolytes at respective individual concentration levels which approximate such major plasma electrolytes and their concentrations.

In the parent hemodialysis one substitutes for 35 the conventional dialysis fluid a solution of the present invention as above characterized in Table VII. Conventional dialysis equipment can be used, but a

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deaerator, such as might tend to eliminate dissolved carbon dioxide from a dialysis solution of this invention, should not be present. During use in peritoneal dialysis, a solution of this invention:

- 5 (a) tends to maintain a normal equivalent ratio of sodium cations to chloride anions, and
- (b) tends to maintain normal cellular and plasma pH, and
- 10 (c) tends to maintain normal cofactor ratios.

The total quantity of such solution of this invention used in a given hemodialysis is comparable to the quantities used in prior art fluids employed under the same conditions (typically from about 35 to 160 liters

15 of dialysis fluid per hemodialysis per man).

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Table VII
Class II Solutions Particularly Suited for
Hemodialysis

5	Component	Composition at Time of Administration	
		Quantity Range	(millimoles per liter)
			broad
10	Total cations (mEq/L)	about 130 to 170	134 to 154
(1) sodium ⁺	about 130 to 155	132 to 145	
(2) potassium ⁺	0 to about 5	0 to 4	
(3) calcium ⁺⁺	0 to about 3	1 to 1.75	
(4) magnesium ⁺⁺	0 to about 2	0.3 to 0.75	
15	Total anions (mEq/L)	about 130 to 170	134 to 154
(5) chloride ⁻	84 to about 125	93 to 115	
(6) bicarbonate ⁻	0 to about 55	25 to 35	
(7) sigma L-lactate ⁻ / pyruvate	0 to about 55	0 to 12	
(8) sigma D-betahydroxybutyrate ⁻ / acetoacetate	0 to about 55	0 to 5	
20	(9) sigma (6+7+8)	about 25 to 55	36 to 42
Total nonionics*	about 0 to 525*	0 to 12	
(10) carbon dioxide	about 0 to 25	0 to 2	
(11) osmotically active substances**	about 0 to 500*	0 to 10	

In Table VII, the component interrelationships are always such that:

(12) mEq. ratio of bicarbonate⁻/
 CO_2

30 (13) mEq. ratio of L-lactate⁻/
pyruvate⁻

(14) mEq. ratio of D-betahydroxybutyrate⁻/
acetoacetate⁻

(15) mEq. ratio of
Na:Cl

35 (16) milliosmolarity of
Solution

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*This upper limit used when the solution is being employed in an old type Kolff kidney where pressure cannot be exerted on the dialysis membrane. In a pressurized dialysis system the limit is 1500 mg. if no anticoagulants are added.

5 is about 0 to 11mMol/l for glucose; if other nonionics are added, then preferred limit would be below about 20 mMol/l total.

**glucose preferred.

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Class II solutions which are within this scope of Table VI above and which are particularly suited for peritoneal dialysis are subgenerically characterized in Table VIII below.

5 Such Class II solutions of Table VIII are suitable for use in a peritoneal dialysis process of the generally known and conventional type when renal function of a living mammal is replaced in whole or in part by dialysis. In peritoneal dialysis a quantity of a dialysis
10 fluid is charged into the peritoneal cavity of such mammal for a time sufficient to achieve a change in the chemical composition of body fluids, after which the dialysate is drained or otherwise removed from the peritoneal cavity. Typical residence times for fluid
15 in the peritoneal cavity range from about 1/2 to 1 hour, although longer and shorter times can be employed. Typically, peritoneal dialysis sessions last 4-1/2 hours, but continuous ambulatory peritoneal dialysis has recently been advocated. The patient's own peritoneum
20 serves as a dialysis membrane. In the conventional peritoneal dialysis procedure, the dialysis fluid is, as in the case of a hemodialysis fluid and aqueous solution which contains dissolved therein the same principal inorganic electrolytes and at respective
25 individual concentration levels which approximate those of major plasma electrolytes and their concentrations, except that in the case of peritoneal dialysis fluids a higher concentration of nonionics, such as glucose, is typically employed in order to provide an osmolarity
30 which is greater than that of mammalian plasma, thereby to promote ion and water transfer through the peritoneum, all as known to those skilled in the art. Chronic, so called "ambulatory" peritoneal dialysis may also benefit from these solutions.
35 In the present invention, one substitutes for the conventional dialysis fluid a solution of the present invention as above characterized in Table VIII. During use in peritoneal dialysis, a solution of this invention:

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65

(a) tends to maintain a normal equivalent ratio of sodium cations to chloride anions,

5

(b) tends to maintain normal plasma and cellular pH,

(c) tends to maintain normal cofactor ratios.

The quantity of such solution employed is comparable to the quantity used in prior art peritoneal dialysis as is the residence time in the peritoneal 10 cavity.

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Table VIII

1
Class II Solutions Particularly Suited for Peritoneal
5 Dialysis

Component	Compositions at Time of Administration	
	Quantity Range	
	(millimoles per liter)	
	broad	preferred
Total cations	about 130 to 170	135 to 150
(1) sodium ⁺	about 130 to 165	130 to 145
(2) potassium ⁺	about 0 to 5	0 to 4
(3) calcium ⁺⁺	about 0 to 2	1 to 1.5
(4) magnesium ⁺⁺	about 0 to 1.5	0.3 to 1
Total anions	about 130 to 170	135 to 150
(5) chloride ⁻	about 81 to 130	93 to 102
(6) bicarbonate ⁻	about 0 to 55	25 to 30
(7) sigma L-Lactate ⁻ /plus pyruvate ⁻	about 0 to 55	2 to 12
(8) sigma D-betahydroxybutyrate ⁻ /		
20 acetoacetate ⁻	about 0 to 55	1 to 5
(9) sigma (6+7+8)	about 26 to 55	36 to 50
Total nonionics*	about 40 to 252	84 to 238
(10) carbon dioxide	about 0 to 25	0 to 2
(11) osmotically	about 40 to 250	83 to 237
25 active substance		
In Table VIII, the component interrelationships are always such that:		
(12) mEq. ratio of HCO ₃ ⁻ /		
CO ₂	about 0.1/1 to 160/1	19/1 to 21/1
30 (13) mEq. ratio of L-lactate ⁻ /		
pyruvate ⁻	about 20/1 to 1/1	10/1 to 5/1
(14) mEq. ratio of D-betahydroxybutyrate ⁻ /		
acetoacetate ⁻	about 6/1 to 0.5/1	3/1 to 1.5/1
(15) mEq. ratio of		
35 Na:Cl	about 1.24 to 1.6	1.36 - 1.42

* glucose preferred

1	(16) Milliosmolarity of Solution	about 310 to 615	350 to 520
	(17) pH of solution	about to 8	7.36 to 7.6

EMBODIMENTS

5 The following examples are merely illustrative of the present invention and are not intended as a limitation upon the scope thereof.

Examples 1 through 27

10 The following compositions of this invention illustrate electrolyte solutions of Class I (above identified) which are suitable for intravenous administration to replace electrolytes and fluid in a human adult patient at dose rates of, for example, 500ml/patient/24 hour day. Each solution consists of water which has dissolved therein each of the identified in the respective specific 15 per liter quantity shown components in the following Table IX.

20 Each solution is here prepared by dissolving substantially pure selected salt and nonionic material following the teaching of "Date for Biochemical Research", 1969, pp.507-508. Each solution can be made from many different materials depending upon manufacturing convenience, ease of sterilization, cost of raw materials, and the like; the only requirement is that the final ionic 25 composition of each solution should be as described.

The footnote for each example in Table IX characterizes the composition and provides a suggested application or use.

Also shown in Table IX are further examples of prior 30 solutions. All solutions are listed as Type 1 a, b, c, and d, in conformity with the classification herein developed.

Table IX Class Ia Solutions Containing 1 or 2 Cations from Among Na^+ , K^+ , Mg^{2+} or Ca^{2+} with no Nutrients (Glucose)
 Case I
 and No $\text{HCO}_3^-/\text{CO}_2$

Units	Normal	1 a 1	1 a 2	1 a 3	1 a 4	1 a 5	1 a 6
Plasma	Normal*	Normal*	Normal*	Isotonic	Isotonic	Isotonic	Isotonic
N.E.J.N.	0.9% NaCl	0.9% NaCl	0.9% NaCl	Malate	Malate/Pyr-	Na BH3/acac	Na BH3/acac
283, 1285	U.S.	U.K.	Salt	Salt	BH3/acac	Salt	Salt
L. fluid	1970						
Na	136 - 145	155	162.5	160.3	153	155	152.5
K	3.5 - 5.0						2.5
Ca free [Ca^{2+}]	2.1 - 2.6						
Mg free [Mg^{2+}]	0.75 - 1.25						
Σ aEq Cations 142.7-153.2 155		162.5	160.3	155	155	155	
Cl	100 - 106	155	162.5	160.3	106	106	106
HCO_3^-	26 - 28						
Cl_1	1 - 1.45						
SO_4^-	0.32 - 0.94						
L - lactate	0.6 - 1.8			52 (d,1)	44	38	
pyruvate				5	5		

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Lact/pyr	0.0	0.8	9.5	
D B Dihbutyrate		4.7	35	
acetoacetate		2.3	14	
B HB/ acac		2.0	2.5	
acetate				
Other				
Σ Eq anions 128.7-139.4	155	162.5	160.3	155
Na/Cl	1.28 - 1.45	1.00	1.00	1.44
Glucose	3.9 - 5.6			
or others	0.99 - 1.39			
CO ₂	7.35 - 7.45	*5.5 - 6.5	*5.5 - 6.5	*6.5
pH				*6.5
Σ osm	265 - 295	310	325	321
Use:	I.V. electrolyte replacement	same as I.V. electrolyte replacement	Used to prevent acidosis	Improves Redox control of Ia1, Ia2 cytoplasm & with K ⁺ with Ca ²⁺ mitochondria
				Alternative

1.a.1. Most common electrolyte solution given in U.S. Tends to cause hyperchlorotic acidosis because of abnormal Na/Cl ratio.

See Black DAK, Lancet i, 553, 1952.

1.a.2. Used in U.K. and Canada.

1.a.3. Darrow et al. J Am Med Ass 143: 365, 432, 1944. Causes redox imbalance.

1.a.4. i - Solutions in boxes are new in this disclosure.

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Table IX. Class 1b Solutions Containing 1 or 2 Cations from Among Na^+ , K^+ , Mg^{2+} , Ca^{2+} with HCO_3^- or $\text{HCO}_3^-/\text{CO}_2$ and No Nutrients.

Units	Normal	1 b 1	1 b 2	1 b 3	1 b 4	1 b 5	7
Plasma	Isotonic	Isotonic	Isotonic	Isotonic	Isotonic	Isotonic	
N.F.J.N.	NaHCO_3^-	$\text{NaHCO}_3^-/\text{CO}_2$	$\text{NaHCO}_3^-/\text{CO}_2 + \text{Malact/pyr}^+$	$\text{NaHCO}_3^-/\text{CO}_2 + \text{Malact/pyr}^+$	$\text{NaHCO}_3^-/\text{CO}_2 + \text{Malact/pyr}^+$	$\text{NaHCO}_3^-/\text{CO}_2 + \text{Malact/pyr}^+$	
203, 1285	Salt	Lact/Py	NaCl + Ca	NaCl + Ca	NaCl + Ca	NaCl + Ca	
1970			$\text{HCO}_3^-/\text{CO}_2$	$\text{HCO}_3^-/\text{CO}_2$	$\text{HCO}_3^-/\text{CO}_2$	$\text{HCO}_3^-/\text{CO}_2$	
Na	136 - 145	169.3	155	153	155	152	
K	3.5 - 5.0					3	
Ca	2.1 - 2.6						
free $[\text{Ca}^{2+}]$	[1.06]						
Mg	0.75 - 1.25						
free $[\text{Mg}^{2+}]$	[0.53]						
Σ Eq Cations	142.7-153.2	160.3	155	155	155	155	
Cl	100 - 106	108.3	106	106	106	106	
HCO_3^-	26 - 28	52	27	27	27	27	
ΣPi	1 - 1.45						
SD_4	0.52 - 0.94						
L - lactate	0.6 - 1.8						
		19	19	13	13	13	

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pyruvate	3	3	2	2
Lact/pyr	6.3	6.3	6.5	6.5
D & L butyrate			5	4
acetoacetate		2.5	3	
BHB/ acac		2.5	1.3	
acetate				
Other				
Σ Eq anions 128.7-139.4	160.3	155	155	155
Na/Cl	1.28 - 1.45	1.48	1.44	1.43
Glucose	3.9 - 5.6			
or others	0.99 - 1.39	1.3	1.3	1.3
CO ₂				
pH	7.35 - 7.45	8.6	7.35	7.35
Σ osm	285 - 295	321	311	311
Use:				

1 b 1. Darrow et al J Am Med Ass 143: 365, 432, 1944, abnormal pH. Incompatible with Mg²⁺ and Ca²⁺.

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Table IX. Class Ic Solutions Containing 1 or 2 Cations from Among Na^+ , K^+ , Mg^{2+} or Ca^{2+} with Non-Ionic Nutrients. Case I

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Lact/pyr	00	7.7	12	5
D & DHButyrate				3.3
acetooacetate			5.3	2
D HB/ acac			2.3	1.65
acetate				
Other				
Eq anions 128.7-139.4	0	54.1	53.4	53.4
NaCl	1.28 - 1.45	-	1.00	1.48
Glucose	3.9 - 5.6	278	195	195
or others				195
CO ₂	0.99 - 1.39			
pH	7.35 - 7.45	*6.5	*6.5	*6.5
005	285 - 295	278	301	302
Use:	fluid replacement + nutrients	same as 1 c 2 + nutrients	NaCl, H ₂ O replacement + calories	Corrects redox imbal- + also for status 1 c 4 epilepticus

* Common non-ionic nutrients are 52, 2.5%, 10% glucose. Additional similar fructose and glycerol solutions in over 20 mM amounts are approved by FDA, but not recommended here. (See "Safe Entry Points")

1 c 1 - Most common I.V. fluid given. *Merck Handbook* 1966, p1867. This is combined with isotonic NaCl in any proportions.

1 c 2 - Used in the U.K. and Canada where "tonic" is different than in the U.S. - reasonably. *Severely Handbook*, 1970, p334.

1 c 3 - 2 parts isotonic glucose plus 1 part isotonic NaCl - *Geigy Handbook* 1970, p 334.

1 c 4 - Prevents hyperchloraemia but causes redox imbalance. *Geigy Handbook* 1970, p 334.

Table IX. Class IC (Cont'd)
Case 1

Units	Normal	11	12	13	14	15
Plasma	Normal	1 c 8	1 c 9	1 c 11	1 c 14	1 c 15
anoles	N.E.J.N.	2L D5W + 0.5L Normal	2L D5W + 0.5L Normal	101 Glucose 2.5% Glucose	D 10 W + D 5 W +	D 5 W +
	285, 1285	with K	0.9% NaCl	+ 0.9% NaCl + 0.45% NaCl	L/P Saline	BH6/Acet + Redox
l. fluid	1970	Saline + Redox	Balance	Saline	Saline	Balance
Na	136 - 145	31	154	154	154	154
K	3.5 - 5.0	5.0				
Ca	2.1 - 2.6					
free (Ca ²⁺)	[1.06]					
Mg	0.75 - 1.25					
free (Mg ²⁺)	[0.53]					
Σ Eq Cations	142.7-153.2	31	154	154	154	154
Cl	100 - 106	22	154	154	105	105
HCO ₃	26 - 28					
z Pi	1 - 1.45					
SO ₄	0.32 - 0.94					
L - lactate	0.6 - 1.0	7				
pyruvate		1	1.43			

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6

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Lact/pyr	7	7	7	7	7
D B Dihbutyrate	0.66	1.57		29	4
acetoacetate	0.33	1.00		20	3
D HB/ acac	2	1.6		1.5	1.3
acetate					
Other					
Σ aEq anions 128.7-139.4	31	36	154	154	154
Na/Cl	1.28 - 1.45	1.41	1.00	1.00	1.47
Glucose	3.9 - 5.6	222.4	278	556	278
or others	0.99 - 1.39				
CO ₂					
pH	7.35 - 7.45	6.5	5.5-6.5	5.5-6.5	5.5-6.5
Σ aEq	285 - 295	284	561	813	293
Use:					

1 c 8. Improves with normal Na/Cl ratio and redox balance the most common routine I.V. order in the U.S.
 1 c 9. Replaces 12.5 aEq of the 40 aEq of K lost / day when given at the usual rate of 2.5L / day.
 1 c 10. Facts and Comparisons Oct '81, p.51, Ippincott, St Louis
 1 c 11. Facts and Comparisons Oct '81, p.51, Ippincott, St Louis
 1 c 12. Facts and Comparisons Oct '81, p.51, Ippincott, St Louis

Table III. Class 1d Solutions Containing 1 or 2 Cations from Among Na^+ , K^+ , Mg^{2+} , or Ca^{2+} plus Non-Ionic Nutrients Plus $\text{HCO}_3^-/\text{CO}_2$

Units	Normal Plasma H.F.J.M. molecules 283, 1285 L. fluid 1970	16 1 d 1 $\text{HCO}_3^-/\text{CO}_2$ Saline + K	17 1 d 2 $\text{HCO}_3^-/\text{CO}_2$ Saline + K	18 1 d 3 $\text{HCO}_3^-/\text{CO}_2$ Saline + Mg	19 1 d 4 $\text{HCO}_3^-/\text{CO}_2$ Saline + Ca	20 1 d 5 $\text{HCO}_3^-/\text{CO}_2$ Saline + K	21 1 d 6 L/P $\text{HCO}_3^-/\text{CO}_2$ Saline + Ca	22 1 d 7 L/P $\text{HCO}_3^-/\text{CO}_2$ Saline HCO_3^- + K	23 1 d 8 Redox Bal. Saline HCO_3^- + 5% Gluc.
Na	136 - 145	155	155	155	155	145	145	141	140
K	3.5 - 5.0	5	5	5	5	4	4	4	4
Ca free (Ca^{2+})	2.1 - 2.6 (1.06)				1.5				
Mg free (Mg^{2+})	0.75 - 1.25 (0.53)				1.0				
Σ Eq Cations	142.7-153.2	155	160	156	158	145	149	141	144
Cl	100 - 106	107	107	107	107	106	106	109	104
HCO_3^-	26 - 28	48	53	49	51	29	29	29	29
2Pi	1 - 1.45								
SO_4^{2-}	0.32 - 0.94								
1 - Lactate	0.6 - 1.8								
pyruvate									
Lact/pyr	7.3	8	7	7	7				

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D B Oilbutyrate	2	2	2	2	2	2
acetobacetate	1	1	1	1	1	1
B HB/ acac	2	2	2	2	2	2
acetate						
Other						
Z Eq anions 128.7-139.4	155	160	156	158	145	149
Na/Cl	1.28 - 1.45	1.45	1.45	1.45	1.37	1.37
Glucose	3.9 - 5.6	10	10	10	10	10
or others	(optional)					
CO ₂	0.99 - 1.39	2.7	2.75	2.71	1.45	1.45
pH	7.35 - 7.45	7.35	7.35	7.35	7.4	7.4
Z 0050	285 - 295	320	330	322	328	290
Use:	Improves normal NaCl	Replaces K loss	Mg ²⁺ does not precipitate leaves patient alkalotic	Ca ²⁺ does not ppt. precipitate as with HCO ₃ ⁻ alone.		

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Table II Class 1d Solutions Containing 1 or 2 Cations, to which is added $\text{HCO}_3^-/\text{CO}_2$ and Non-ionic Nutrients
Case I (Cont'd)

	24	25	26	27
Units	Normal 1 d 9 2L D5W	1 d 10 2L D5W	1 d 11 R.B. Saline Like 1d11	1 d 12
anoles	N.F.J.M. + 0.5L R.B. + 0.5L R.B. with K 4 but BHB acid			
-----	2B3, 12B5	Saline	Saline + K	
L fluid	1970		2.5% Gluc. & added to make No added CO_2 CO_2 in situ	
Na	136 - 145	28.2	28.2	140
K	3.5 - 5.0		5	4
Ca	2.1 - 2.6 free [Ca2+] [1.06]			
Mg	0.75 - 1.25 free [Mg2+] [0.53]			
$\Sigma \text{Eq Cations}$	142.7-153.2	28.2	33.2	144
Cl	100 - 106	20	20	104
HCO_3^-	26 - 28	5.8	10.8	29
ΣPi		1 - 1.45		
SO_4^-	0.32 - 0.94			
L-lactate	0.6 - 1.8	1.4	1.4	5
pyruvate	0.2	0.2	1	1

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Lact/pyr	7	7	7	7
D Dihydroxybutyrate	0.4	0.4	2	1
acetoacetate	0.2	0.2	1	1
D Hb/ acat	2	2	2	2
acetate				
Other			• 2 Lactate + 2 D Dihydroxybutyric acid	
Σ Eq anions 120.7-139.4	28.2	35.2	144	144
Na/Cl	1.28 - 1.45	1.41	1.41	1.35
Glucose	3.9 - 5.6	222.4	139	139
or others	0.99 - 1.39	0.29	0.54	0 -
CO_2				
pH	7.35 - 7.45	7.4	7.4	7.4
Σ mEq	285 - 295	279	289	277
Use:		Replaces & Replaces		
		21 D5W & K loss		
		0.51 Normal		
		Saline		

1 d 11 • Lactic acid is added instead of CO_2 to generate CO_2 in situ.1 d 12 • D Dihydroxybutyric acid is added to generate CO_2 in situ.

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Examples 28 through 41

1 The following compositions of this invention
illustrate electrolyte solutions of Class II (above
identified) which are suitable for (a) intravenous use
5 to replace electrolytes and fluid (b) providing parenteral
nutrition in a human adult patient, (c) peritoneal
dialysis, and (d) hemodialysis. Dose rates can vary.
Each solution consists of water which has dissolved
therein each of the identified components in the respec-
10 tive specified concentrations per liter quantity shown
in the following Table X. Each solution is prepared by
conventional procedures. (See text of Examples 1 through
27).

15 The footnote for each example in Table X charac-
terizes the composition and provides a suggested appli-
cation or use.

20 These compositions demonstrate, as do Tables V
through VIII (above), that there is no essential
compositional difference between these various
solutions.

25 Table XI shows prior art hemodialysis fluids for
comparison purposes in dialyzing a human adult patient
using, for example, an apparatus as described by
Miller J.H., Schinaberger J.H., Kraut J.A., and
Gardner P.S., Trans. Am. Soc. Artif. Intern. Organs 25,
404-408, 1979.

30 In these solutions which contain dissolved CO₂,
no deaerator should be used on the dialysis equipment.

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Table I Class 2a Electrolyte Fluids Containing 3 or 4 Cations Suitable for Contracting Cells, Containing No HCO_3/CO_2 and No Glucose; e.g. after S.J. Ringer, *Physiol. Rev.* 4: 29, 223, 1885, and 7: 291, 1886.

		20	29	30
Units		2. a. 1. Ringer's Plasma	2. a. 2. Lactated Ringer's Injection	2. a. 3. Acetated Ringer's (Commercial) U.S.
moles	N.F.J.M. 283, 1285	U.S.	U.S.	U.S.
L. fluid	1970			
Na	136 - 145 * (137-145)	147	129.8	130
K	3.5 - 5.0	4	5.4	4
Ca	2.1 - 2.6 free [Ca2+] 1.06]	2.5	0.9	1.5
Mg	0.75 - 1.25 free [Mg2+] 0.53]		1.0	1.5
$\Sigma \text{Eq Cations}$	142.7-153.2	156	139	137
Cl	100 - 106 * (100-110)	156	111.0	109
HCO_3	26 - 28			
ΣPi		1 - 1.45		
SO_4	0.32 - 0.94			
L - lactate	0.6 - 1.8		27.2 (d,1)	28 (d,1)
pyruvate			27.5 (d,1)	35.9
				5.1

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Lact/pyr	00	00	00	7	7.5
D B OHbutyrate				27.3	5
acetacetate				13.7	2
B Hb/ Acac				2	2.5
acetate				27.5	
Other					
Σ Eq anions	128.7-139.4	156	139	137	158
Na/Cl	1.28 - 1.45	0.94	1.16	1.19	1.36
Glucose	0(1.245-1.45)				
or others	3.9 - 5.6				
CO ₂	0.99 - 1.39				
pH	7.35 - 7.45				
Σ osm	285 - 295	309	276	272	312
Use:	I.V. fluid	I.V. fluid	I.V. fluid	I.V. fluid	I.V. fluid
	Improves	Improves	Improves	Improves	Improves
	2 a 3.	2 a 4	2 a 3.	2 a 4	2a3, 2a6,
					2a7.

2a7.

W.J.H. Path & Blood Bank Guide, Revised Nov 1, '82.

2. a. 1. Facts and Comparisons p50, Oct '81, Lippincott

2. a. 2. Hartmann AF. *J. Am. Med. Ass.* 103: 1349, 1934.

2. a. 3. Facts and Comparisons p50, Oct '81, Lippincott. Widely used in blood product administration and surgery.

2. a. 4. Facts and Comparisons p50, Oct '81, Lippincott.

2. a. 5. Fox et al. *J. Am. Med. Ass.* 148: 827, 1952. Corrects abnormal Na/Cl ratio but by use of pathogenic organic anions.

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Table X Class 2a Electrolyte Fluids Containing 3 or 4 Cations Suitable for Contracting Cells, Containing No $\text{HCO}_3^-/\text{CO}_2$ and No Glucose; eq. after S.J. Ringer, *Physiol* 4: 29, 223, 1883, and 7: 291, 1886.

Units	Normal Plasma	2. a. 1. Ringer's Injection U.S.	2. a. 2. Lactated Ringer's	2. a. 3. Acetated Ringer's	2. a. 4. Lact/Pyr Ringer's	2. a. 5. Lact/acet Ringer's	2. a. 6. dB-HB/acet Ringer's	2. a. 7. Redox Balanced Ringer's	2. a. 8. Ringer's
moles	N.F.J.N.	283, 1285	U.S.						
L. fluid	1970								
Na	136 - 145 *1137-1451	147	129.0	130	130	140	130	130	130
K	3.5 - 5.0	4	5.4	4	4	10	4	4	4
Ca free $[\text{Ca}^{2+}]$ [1.06]	2.1 - 2.6	2.5	0.9	1.5	1.5	2.5	1.5	1.5	1.5
Mg free $[\text{Mg}^{2+}]$ [0.53]	0.75 - 1.25		1.0			1.5			
2 aEq Cations	142.7-153.2	156	139	137	137	158	137	137	137
Cl	100 - 106	156	111.8	109	109	103	96	96	96
HCO_3^-	*1100-1101 26 - 28								
ΣPi	1 - 1.45								
SO_4^-	0.32 - 0.94								
L - lactate	0.6 - 1.0		27.2 (d,1)	28. (d,1)		27.5 (d,1)	35.9	30	4
pyruvate		00	00			5.1		7.5	7
Lact/pyr		00	00			00			

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D B	0	B	0	Butyrate	27.3	5
acetoacetate					13.7	2
D HB/	acac				2	2.5
acetate			28	27.5		
Other						
Σ Eq anions	128.7-139.4	158	139	137	137	137
Na/Cl	1.28 - 1.45	0.94	1.16	1.19	1.36	1.35
Glucose	4(1.245-1.45)					
or others	3.9 - 5.6					
CO ₂	0.99 - 1.39					
pH	7.35 - 7.45					
Σ 0.058	285 - 295	308	276	272	312	272.5
Use:	1.V. fluid	I.V. fluid	I.V. fluid	I.V. fluid	Improves	Improves
					2 a 3.	2 a 4
						2 a 7.

2. a. *H. J. H. Path & Blood Bank Guide*, Revised Nov 1, '82.
 2. a. 1. *Facts and Comparisons* p50, Oct '81, Lippincott
 2. a. 2. *Hartmann AF. J. Am. Med. Ass.* 103: 1349, 1934.
 2. a. 3. *Facts and Comparisons* p50, Oct '81, Lippincott. Widely used in blood product administration and surgery
 2. a. 4. *Facts and Comparisons* p50, Oct '81, Lippincott.
 2. a. 5. *Fox et al. J. Am. Med. Ass.* 148: 827, 1952. Corrects abnormal Na/Cl ratio but by use of pathogenic organic anions.

Table X. Class 2a (Cont'd) Solutions with Bold numbers and in boxes are new disclosures.

Units	Normal Plasma N.E.J.M. anoles L fluid	2 a 9 Redox Balanced Ringer's 1970	2 a 10 Ionomosol D-CW Ringer's High K	2 a 11 Plasmasalite (Travenol) (Abbott)	2 a 12 Isolyte S (McGaw)	2 a 13 Isolyte E (McGaw)	2 a 14 Delbecco's Pi Buffered Saline	2 a 15 Krebs Ringer Phosphate (Cutter)
Na	136 - 145	140	138	140	140	140	152	150.76
K	3.5 - 5.0	10	12	10	5	10	4.17	5.92
Ca	2.1 - 2.6 free [Ca2+] [1.06]	1.0	2.5	2.5	2.5	0.9	2.54	
Mg	0.75 - 1.25 free [Mg2+] [0.53]	0.5	1.5	1.5	1.5	0.45	1.18	
2 a Eq Cations	142.7-153.2	153	158	148	158	159.15	164.12	
Cl ⁻	100 - 106	103	108	103	98	103	140.5	131.51
HCO ₃ ⁻	26 - 28						9.8	17.38
Z Pi	1 - 1.45						0.45	1.18
SO ₄ ²⁻	0.32 - 0.94							
L - lactate	0.6 - 1.0							
pyruvate		5						
Lact/pyr	7.6	00						

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0.9 Dihbutyrate	5					
acetooacetate	2					
0.9 HB/ acac	2.5					
acetate	47	27	49			
Other		23	glutonate 4 citrate			
Σ Eq anions 128.7-139.4	153	158	148	158	159.18	163.97
Na/Cl	1.28 - 1.45	1.36	1.36	1.43	1.40	1.08
Glucose	3.9 - 5.6					
or others	0.99 - 1.39					
CO ₂						
pH	7.35 - 7.45				7.4	7.4
Σ anions	285 - 295	304.5	312	294	315	308.3
User		Improves I.V. electrolyte 2 a 10 2 a 5, lowers Ca & therapy Mg to normal				
		Same as Same as redox imbalance				
		PPi accumulation NADP/NADPH				
		Tissue culture imbalance of salt mix				
		NADP/NADPH				

2 a 10. Facts and Comparisons Oct '81, p 50
 2 a 11. Facts and Comparisons Oct '81, p 50
 2 a 12. Facts and Comparison Oct '81, p 50
 2 a 13. Facts and Comparisons Oct '81, p 50
 2 a 14. Delbecco R, Vogt M. *J Exp Med* 99: 167-182, 1954
 2 a 15. Krebs HA. *Hoppe-Seyler's Z Physiol Chem* 217: 193, 1933

Table X. Class 2b Electrolyte Fluids Containing 3 to 4 Cations Suitable for Contacting Cells Also Containing $\text{HCO}_3^-/\text{CO}_2$ and No Glucose after Krebs HA & Henseleit KA, Hoppe-Seyler's Z Physiol Chem 210: 33-66, 1932.

Units	Normal Plasma	2 b 1 Krebs	32 2 b 2 Redox Bal- anced	33 2 b 3 Redox Bal- anced	34 2 b 4 High HCO_3^- Ringer's	35 2 b 5 L/P Ringer's	36 2 b 6 Ketones
moles	H.E.J.M.	Henseleit					
	203, 1205						
	1970						
L fluid							
Na	136 - 145	143	130	136	136	130	130
K	3.5 - 5.0	5.9	4	4	4	4	
Ca free $[\text{Ca}^{2+}]$	2.1 - 2.6	2.5	1.5	1	1	1.5	1.5
Mg free $[\text{Mg}^{2+}]$	0.75 - 1.25	1.2		0.5	0.5		
Z Eq Cations	142.7-153.2	156.3	137	143	143	137	137
Cl	100 - 106	127.8	96	100	100	96	96
HCO_3^-	26 - 28	25	29	29	43	29	29
pH	1 - 1.45	1.10					
SO_4^-	0.32 - 0.94	1.2					
L - lactate	0.6 - 1.8		7	9		10.5	
pyruvate			1	1		1.5	

	7	9	7	8
Lact/pyr	3	3		
0.8 Dibutyrate	1	1		
acetoacetate			4	
BHB/ acac	3	3		
acetate			2	
Other				
Σ mEq anions 128.7-139.4	137	143	137	137
Na/Cl	1.28 - 1.45	1.12	1.35	1.35
Glucose	3.9 - 5.6			
or others	0.99 - 1.39	1.24	1.5	1.5
CO_2			2.46	1.5
pH	7.35 - 7.45	7.4	7.4	7.4
Σ osm	285 - 295	308	286	274
Use:				
	To replace	For blood	For Rx of	Alternate
	all previous replace-	acidosis	Lactated	to 2 b 2
	ment		Ringer's	to 2 b 5
	organ			
	perfusion			

2 b 2 to 2 b 6. All these solutions would be suitable, given added glucose, for peritoneal dialysis, ie like class 2 c.

As it is, these solutions would improve existing haemodialysis.

Table X. Class 2c Electrolyte Fluids Containing 3 or 4 Cations Suitable for Contracting Cells Containing No $\text{HCO}_3^-/\text{CO}_2$ to which are Added Non-ionic nutrients such as Glucose, Fructose, Glycerol etc.

Units	Normal Plasma N.F.J.M.	2 c 1 Lactated Ringer's Glucose	2 c 2 1/2 Strength Lactated Ringer's Glucose	2 c 3 Acetated Ringers 5% Glucose	2 c 4 Dialysed Ringers 5% Glucose	2 c 5 Dialysed Glucose	2 c 6 Dialysed Glucose	2 c 7 Dialysed Glucose
anoles	283, 1285 1970							
L Fluid								
Na	136 - 145	130	65	130	57	141	141.5	132
K	3.5 - 5.0	4	2	4	25			4
Ca free [Ca2+] [1.06]	2.1 - 2.6	1.5	0.75	1.5		1.75	2.0	1.875
Mg free [Mg2+] [0.53]					2.5	0.75	0.75	0.75
2 Eq Cations 142.7-153.2 137		69.5	137	87	146	147	141	
Cl	100 - 106	109	55	109	49	101	102.5	106
HCO_3^-	26 - 28							
Z Pi	1 - 1.45							
SO_4	0.32 - 0.94							
L - Lactate	0.6 - 1.8	28 (d,1)	14 (d,1)	25 (d,1)	45 (d,1)	35 (d,1)		
pyruvate								

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Lact/pyr	00	00	00	00	00	00
D B β butyrate						
acetoacetate						
D NB/ acac						
acetate	28				44.5	
Other						
Z eq anions 128.7-139.4	137	69	137	87	146	147
NaCl	1.28 - 1.45	1.19	1.18	1.19	1.16	1.40
Glucose	3.9 - 5.6	278	139	278	278	83
or others						
CO ₂	0.99 - 1.39					
pH	7.35 - 7.45					
Z osm	285 - 295	524?	263	523	443	366
		4 (550.5)				
Use:	I.V. therapy I.V. therapy I.V. therapy Parenteral for dehydr- same as same as nutrition ation	2 c 1	2 c 1	2 c 1	2 c 1	2 c 1

* 2 c 1. Facts and Comparisons Oct '81, p 52. The osmolarity listed by the reference appears to be incorrect at 524 osm.

The correct osmolarity appears to be 550.5 osm.

2 c 2 - 2 c 3. Facts and Comparisons Oct '81, p52. Lippincott, St Louis

2 c 4. Facts and Comparisons Oct '81, p52. Lippincott, St Louis

2 c 5 - 2 c 7. Facts and Comparisons Oct '82, p704, Lippincott, St Louis

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Table X. Class 2c (Cont'd)

Units	Normal Plasma	37	38
		2 c 8	2 c 9
	L/P, BHB/Acet NaCl, L/P		
Medes	W.F.J.M.	Ringer's	Balanced
	285, 1285	51 Gluc	Ringer's
L. fluid	1970	51 Gluc	51 Gluc
Na	136 - 145	130	130
K	3.5 - 5.0	4	4
Ca	2.1 - 2.6	1.5	1.5
free [Ca ²⁺]	[1.06]		
Mg	0.75 - 1.25		
free [Mg ²⁺]	[0.53]		
Z Eq Cations	142.7-153.2	137	137
Cl	100 - 106	104	96
HCO ₃	26 - 28		
Σ Pi	1 - 1.45		
SO ₄	0.32 - 0.91		
L - lactate	0.6 - 1.8	24.5	35.9
pyruvate		3.5	5.1

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Lact/pyr	7	7
0.9 Dibutylrate	3	
acetoacetate	2	
BHB/ acac	1.5	
acetate		
Other		
2 Eq anions 128.7-139.4	137	137
Na/Cl	1.28 - 1.45	1.24
Glucose	3.9 - 5.6	218
or others		278
CO ₂	0.99 - 1.39	
pH	7.35 - 7.45	
2.05a	285 - 295	550.5
Use:	Improved 2 a b	
	2 c 1, with Gluc.	
	redox bal-	Normal BHB/Acac
	ance and	normal
	normal	Na/Cl ratio
	Na/Cl	

Table I. Class 2d Electrolyte Fluids for Contacting Living Cells Containing 3 to 4 Cations plus Non-Ionic Nutrients plus HCO_3/CO_2

Units	Normal Plasma	2 d 1 Krebs N.E.J.M.	2 d 2 Tyrode's Serum Substitute	39		40		41	
				Yeech's Redox Balanced Salt Solution	Veech's Redox Balanced Salt Solution	2 d 3 Yeech's Redox Balanced Salt Solution	2 d 4 Yeech's Redox Balanced Salt Solution	2 d 5 Yeech's Redox Balanced Salt Solution	
anoles	203, 1285								
Li fluid	1970								
Na	136 - 145	141	151.54	142	140.4	141			
K	3.5 - 5.0	5.93	5.9	4.5	4.5	4			
Ca	2.1 - 2.6	2.54	1.8	1.1	1.1	1.1			
free $[\text{Ca}^{2+}]$ [1.06]				[1.06]					
Mg	0.75 - 1.25	1.18	0.45	0.56	0.56	0.56			
free $[\text{Mg}^{2+}]$ [0.53]				[0.53]					
$\Sigma \text{MEq Cations}$	142.7-153.2	154.37	162.07	149.82	148.2	149.3			
Cl	100 - 106	104.8	147.8	102	102	102			
HCO_3	26 - 28	24.9	11.9	29	29	29			
Z Pi	1 - 1.45	1.33	1.220	1.10					
SO_4	0.32 - 0.94	2.36		[0.71]					
L - lactate	0.6 - 1.8		1.33		10.7	10.7	10.8		
pyruvate		4.9	0.09		1.5	1.5	1.5		

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Lact/pyr	-	14.8	7	7	7
D 8 Dihbutyrate		3	3	3	3
acetoacetate		2	2	2	2
D HB/ acac		1.5	1.5	1.5	1.5
acetate					
Other		2.45 glutamate			
		5.4 fumarate			
Σ Eq anions 128.7-139.4	154.47	162.81	149.82	148.2	148.3
Na/Cl	1.28 - 1.45	1.35	1.03	1.39	1.38
Glucose	3.9 - 5.6	9.2	5.45	10	277
or others	0.99 - 1.39	1.0	1.17	1.45	1.45
CO ₂					
pH	7.35 - 7.45	7.4	7.1	7.40	7.40
Σ osm	285 - 295	308.2	328	308.6	306.4
Use:					
	Media for	For liver	For I.V. or for perito-		
	tissue	perfusion	general use		
	slices		peritoneal		
			dialysis		
			to replace		
			or I.V.		
			dialysis		
			2 b 1 & 2 d 1		

2 d 1. Krebs HA. Biochen Biophys Acta 4: 249-269, 1950

2 d 2. Tyrode MJ. Arch int Pharmacodyn 20: 205, 1910. * For use in liver perfusion with albumin see Schiasssek H. Biochen 2 336:460,1963

2 d 3. * The apparent charge on suc Pi in the presence of these cations is about 1.46 not 1.0 presumably due to cation binding.

Table XI. Prior Art Hemodialysis Fluids. For recent discussion see Parsons FH, Stewart MK. Composition of Dialysis Fluid. In: Replacement of Renal Function by Dialysis (Drucker W, Parsons FH, Maher JP, eds.) Martinus Nijhoff,ingham, pp 146-170, 1983.

Units	Norval	2 d b	2 d 7	2 a 16	2 a 17	2 a 18	2 a 19	2 b 2	2 b 3
Plasma	Kolff	Brigham	Scribner's	Commercial	Bjaeldner	Bjaeldner	Bjaeldner	Globe	Globe
anoles	N.E.J.H.	1947	1952	Acetate	"Low" Acet.	"Low" Acet.	"High" Acet.	Kraut	Kraut
-----	283, 1285			1964	1981	1981	1981	HCO ₃ -Acetic	HCO ₃ -Acetic
L fluid	1970							Acid	Acid
Na	136 - 145	126	140	135	140	134	136	140	135
K	3.5 - 5.0	5.6	4	1.5	2	2.2	2.2	2	2
Ca	2.1 - 2.6	1.0	1.25	1.25	0.875	1.84	1.91	1.75	1.5
free [Ca ²⁺] [1.06]									
Mg	0.75 - 1.25		0.5	0.5	0.375	0	0	-	0.375
free [Mg ²⁺] [0.53]									
Eq Cations	142.7-153.2	133.6	147.5	140	144.5	139.88	142.02	145.5	140.75
Cl	100 - 106	109	120.7	105	106	107.28	103.82	107	106.5
HCO ₃	26 - 28	23.9		26.8				33	33
Pi		1 - 1.45							
SO ₄			0.32 - 0.94						
L - lactate	0.6 - 1.8								
pyruvate									

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	acetate	35	38.5	32.6	38.2	2.4acetate	2.4acetate
acetooacetate							
0 HB/ acac							
Other							
eq anions 128.7-139.4	132.9	147.5	140	144.5	139.88	142.02	145.5
Na/Cl	1.28 - 1.45	1.16	1.16	1.29	1.32	1.25	1.31
Glucose	3.9 - 5.6	7.6 - 15.1	10	0	0	0	0
or others	0.99 - 1.39	0	1.24	0	0	0	0
CO ₂							
pH	7.35 - 7.45	78.6	7.4	75.5-6.5	75.5-6.5	76.7	77.4
atm	285 - 295	343 - 418	304.0	278.25	287.75	277.92	282.97
						289.3	280.4
2 d 6. Kalf WJ. <i>New Ways of Treating Uremia</i> , JJA Churchill, London, 1947							
2 d 7. Murphy MP, Saan RG, Walter C, Weller JH, Merrill JP. <i>J Lab Clin Med</i> 40: 436, 1952. Essentially Krebs Venolexit, but with lower Mg and Ca.							
2 a 16. Miron CM, Hegstrom RM, Boen SJ, Scribner BH. <i>Trans Am Soc Artif Intern Organs</i> 10: 110-113, 1964							
2 a 17. Made in concentrates by numerous manufacturers. The mean concentrations used are given in 2 d 17 according to Parsons FM and Stewart WK, listed above in title.							
2 a 18. Bjaelder et al <i>Nedros 23</i> : 142-145, 1981. "Low" acetate leaves the patients acidotic, "high" acetate leaves them in normal. Bjaeelder's interpretation for the reasons for the acidosis are incorrect.							
2 b 6. Kraut J et al. <i>Clin Neph</i> 15: 181, 1981. Used HCO ₃ and acetic acid.							
2 b 3. Commercial source. CDBE Laboratories, 1201 Oak Street, Lakewood Colorado.							

EXAMPLE 42

1 The following example illustrates usage of Class I
solutions for electrolyte and fluid therapy.

5 The most commonly used electrolyte solution used
today, by those skilled in the art, is so called
"physiological" salt, or "normal saline" by which is
means 0.9% NaCl in H₂O in the U.S. or 0.95% NaCl in
H₂O in the United Kingdom. (See Table IX solutions 1a1
and 1a2 respectively). These solutions, wherein the
10 milliequivalent ratio of Na/Cl is 1, are distinctly dif-
ferent from normal human plasma wherein the ratio of
Na/Cl ranges from 1.28 to 1.45 (N.E.J.M. 283, 1285, 1970).
Infusion of such solutions has long been recognized
15 to be undesirable leading to a pathological condition known
as "hyperchloremic acidosis". (See Black D.A., Lancet 1,
353, 1953, and Harrison's Textbook of Medicine, pp 230
to 236, 1983). The degree of the pathology induced by
solutions where the ratio of Na/Cl is below the ratio
1.28-1.45 depends upon:

20 1) the quantity of solution infused relative to
the volume and electrolyte content of the
extra-and intracellular H₂O volume of the
cells being contacted;

2) the rate of infusion of solutions;

25 3) the degree of existing pathology in the
organism being contacted with such fluid;

4) the efficiency of the kidney in excreting the
excess of Cl⁻ and Na⁺ being administered.

30 In this example, the replacement of plasma H₂O
and salt content in the rat serves as a model stimulating
the situation which might occur in a human patient when
a severe burn over 50% of the body exists resulting in
the loss of plasma H₂O and electrolytes into transudates
and blisters over the surface of damaged skin. Three
35 solutions for therapy will be used: standard 0.9%

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1 aqueous NaCl (composition 1a1 of Table IX), standard
lactated Ringer's U.S. (composition 2a3 of Table X) and
a modified redox-balanced Ringer's Lactate solution
containing, with near-equilibrium couples, (l-lactate⁻/
5 pyruvate⁻ and D-betahydroxybutyrate⁻/acetoacetate⁻),
HCO₃⁻/CO₂ (composition 2b2 of Table X)
in accord with the present invention. The composition
of the 3 fluids are given in Table XIII below.

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(Electro2)

Table VIII - Composition of Fluids

Units	Normal Plasma	1:1 N.F.J.A. NaCl	1:1 NaCl	2:3 Lactated Ringer's	2:2 R-R Lactated Ringer's HCO ₃ /CO ₂
mmoles					
Na	136 - 145	155	130	130	
K	3.5 - 5.0	4	4	4	
Ca	2.1 - 2.6	1.5	1.5	1.5	
free [Ca ²⁺] [1.06]					
Mg	0.75 - 1.25				
free [Mg ²⁺] [0.53]					
Σ Eq Cations	142.7-153.2	155	137	137	
Cl	100 - 106	155	109	96	
HCO ₃	26 - 28			29	
Σ Pi	1 - 1.45				
SO ₄		0.32 - 0.94			
L-lactate	0.6 - 1.8		26 (d,l)	7	
pyruvate				1	
Lact/pyr		00		7	

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D B Dihutyrate	3		
acetoacetate	1		
B Hb/ acac	3		
acetate			
Other		1.37	
Σ Eq anions	128.7-139.4	155	137
Na/Cl	1.28 - 1.45	1.00	1.19
			1.35
Glucose	3.9 - 5.6		
or others	0.99 - 1.39		
CO ₂			1.5
pH	7.35 - 7.45	6.0	6.5
			7.4
Σ Bic	285 - 295	310	272

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1 METHODS

250 fed male Wistar rats are each anesthetized and systematically burned with gasoline over approximately the lower 50% of the body surface. A blood sample is taken from each rat prior to administration of the burn, and then again two hours after the burn from a venous canula inserted into the saphenous vein. Each animal is placed in a restraining case.

In the opposite saphenous vein, a canula is inserted to measure plasma electrolyte content. Five minutes after the administration of each electrolyte solution, blood is drawn for electrolyte analysis. Each rat's liver is removed, freeze clamped and the redox and phosphorylation states of liver measured by the methods previously described by Veech et al. (J. Biol. Chem. 254, 6538-6547, 1979).

15 RESULTS AND DISCUSSION

It is observed that 1/2 hour after the gasoline burn, a series of weeping blisters develop over the lower 1/2 of each rat's body. The volume of the transudate within these blisters is estimated by measurement of area and thickness to contain 4ml of transudate or ($250 \times 0.07 = 17.5$ ml blood volume) or about 40% of the rat's average total plasma volume. This deduction is confirmed by measurement of the rat hematocrit which is 55% while the Na^+ is 155 millimoles per liter plasma and Cl^- is 110 millimoles per liter plasma due to fluid loss. In the untreated controls rats, the hematocrit is 44%. Each treated animal's blood pressure is falling, heart rate is increasing, and urine output ceases.

Each treated animal is judged to be in hypo-volemic shock and 6mls of the three different solutions are infused, by venous canula, over the next 10 minutes, into three different animals.

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- 1 Five minutes after completion of the infusion, electrolytes are drawn from the canula, the animals sacrificed, and the liver freeze clamped. The average blood electrolyte level, in each of the three groups of animals so infused, is shown in Table XIV below.

Table XIV Composition of Plasma After Infusion

Units m moles/ L fluid	Normal Plasma H.E.J.H. 283, 1285, 1970	1a1 Isotonic NaCl	2a3 Lactated Ringers	2b2 R-B Lactated Ringers HCO ₃ ⁻ /CO ₂
Na	135-145	150	143	138
K	3.5-5.0	5	5	5
Ca free [Ca ²⁺]	2.1-2.6 [1.06]	2.0	2.2	2.5
Mg free ²⁺ [Mg ²⁺]	0.75-1.25 [0.53]	1.0	1.0	1.0
Σ meq Cations	142.7-153.2	158	153.2	147.5
Cl	100-106	123	105	102
HCO ₃ ⁻	26-28	18	13	27
Σ Pi	1 - 1.45	1.5	1.2	1
L-lactate	0.6-1.8	5.0	21	5
pyruvate		0.3	1.0	0.7
Lact/pyr			21	7
D-E-OH butyrate				0.7
acetoacetate				3
BHE/acac				
acetate				
others				
Σ meq anions	128.7-139.4	146.3	141.2	138.65
Na/Cl	1.28-1.45	1.22	1.34	1.36
Glucose or others	3.9-5.6	8.2	10	7
CO ₂	0.99-1.39	1.14	0.82	1.35
pH	7.35-7.445	7.30	7.30	7.4
Σ m Osm	285-295			

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1 Having now fully described the invention, it will be
apparent to one of ordinary skill in the art that many
changes and modifications may be made thereto without
departing from the spirit or scope of the invention as
5 set forth herein.

It is observed that the animals given 1a1 (0.9% saline) solution each have hyperchloremic acidosis with a Na/Cl ratio of 1.22 and plasma pH of 7.30. The animals given solution 2a3 Ringer's Lactate solution 10 each have lactic acidosis with a plasma pH of 7.3 and an elevated [lactate]/[pyruvate] ratio. Both groups of these animals have low serum $[HCO_3]$ and have a compensated metabolic acidosis which requires that they hyper-ventilate off their CO_2 . In contrast, the animals given 15 solution 2b2 (Redox-balanced Ringers Lactate with HCO_3/CO_2) each have a normal [lactate]/[pyruvate] ratio, a normal $[HCO_3]/[CO_2]$ ratio and a normal plasma pH. More importantly, each of these animals achieves a replacement of H_2O and electrolytes as required for 20 continued life, but without inducing an abnormal Na/Cl ratio, an abnormal redox state, or an abnormal phosphorylation potential. No change in respiratory pattern is observed in the grave life-threatening situation. Solution 2b2 is then an improvement over the 25 state of the art.

In Table 3 is given the results of the freeze clamp-ing of the liver to illustrate the effects of these solutions on the nucleotide ratios in liver cells. These results indicate that only in the liver cells of the 30 rats treated with the redox-balanced Ringer's lactate solution (Table X, solution 2b2) of this invention do these ratios approach normal values. Here, it is seen that administration of Na/Cl in 1:1 ratio leads to no change in the cytoplasmic [NAD]/[NADH] but does cause 35 an increase in the cytoplasmic [ATP]/[ADP][Pi]. With

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1 no intention to be bound by theory, the elevation of
[ATP]/[ADP][Pi] would be expected from equation 7 given
in another section. The conventional Ringer's lactate
2a3 gives a profound and pathological decrease in
5 the cytoplasmic $[NAD^+]/[NAD]$ to levels associated with
alcoholic fatty liver. There is, of course, a
predictable falls in the [ATP]/[ADP][Pi], since the
redox state of the cytoplasmic NAD-couple is directly and
inversely linked to the cytoplasmic [ATP]/[ADP][Pi]
10 ratio as equation 5 shows.

In contrast, the new Redox Balanced Ringer's Lactate solution of the present invention does not change the cytoplasmic $[NAD^+]/[NADH]$ from out of the normal range and causes no change in the [ATP]/[ADP][Pi].
15 Replacement of needed H_2O and electrolytes has been accomplished without inducing acidosis or any other recognized pathologic effects which can be demonstrated by using NaCl in 1:1 ratio or standard Ringer's Lactate in this simulation of a very common
20 clinical situation.

Example 42
Case 1Table XV. Metabolite Contents of Freeze-Clamped Rat Liver in Rats After Infusion with Normal Saline, Ringer's Lactate, and Redox Balanced Ringer's Lactate with $\text{HCO}_3^-/\text{CO}_2$

Values are in umoles/g wet weight.

	Normal Rat	0.9% NaCl Infusion Solution	1.a.1	Ringer's Lactate 2.a.3	New R-B Ringer's Lactate with $\text{HCO}_3^-/\text{CO}_2$ 2.b.2
Glucose	7.3	8.0	13	8	
Glucose 6-F	0.12	0.18	0.26	0.16	
Dihydroxy- acetone-F	0.029	0.051	0.078	0.039	
3-Phospho- glycerate	0.309	0.369	0.56	0.35	
L-Lactate	0.444	0.812	14.8	5.2	
Pyruvate	0.086	0.165	0.70	0.74	
L-Lactate/pyr	5.16	4.92	21	7.00	
3-PG/DHAF	10.65	7.24	7.14	8.93	

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Example 42
Case 1Table XVI Co-Factor Ratios of Freeze-Clamped Liver of Rat After Infusions with 0.9% Normal Saline, Ringer's Lactate, and Redox-Balanced Ringer's Lactate with $\text{HCO}_3^-/\text{CO}_2$

	Normal Rat	0.9% NaCl Infused Rat 1.a.1	Ringer's Lactate Infused Rat 2.a.3	New R-B Ringer's Lactate with $\text{HCO}_3^-/\text{CO}_2$ 2.b.2
Free Cytoplasmic [NAD ⁺]/[NADH]	1750	1790	429	1290
Free Cytoplasmic $\frac{[\Sigma \text{ATP}]}{[\Sigma \text{ADP}][\Sigma \text{Pi}]}$ M ⁻¹	14,000	20,900*	5,000*	12,000

* indicates change is significant at $p < 0.05$.

1

Example 43

Use of Solutions for Parenteral Nutrition

The procedure used is identical to that utilized by Woods, Eggleston and Krebs in Biochem. J. (1970) 119, 5 501-510.

Animals and Diets

Female Wistar rats, each weighing 170-215g, are obtained and are fed on a standard small-animal diet.

Reagents

10 D-Glyceraldehyde, L- -Glycerophosphate (dicyclohexyl-ammonium salt) having a purity of 96% of the calculate L-form and other substances, nucleotides, coenzymes, and crystalline enzymes.

Liver Perfusion

15 The method of liver perfusion used is that described by Hems, Ross, Berry & Krebs (1966). The perfusion medium is the physiological saline (Krebs & Henseleit, 1932), containing washed aged human erythrocytes. The bovine serum albumin is dialyzed as a 10% solution (at 20 4°C) against three changes of physiological saline (Krebs-Henseleit) and gassed with $\text{CO}_2 + \text{O}_2$ (5:95).

The perfusion medium described by Hems et al. (1966) is used, which contains initially about 1 mM L-lactate [0.87 ± 0.05 S.E.M. (14) $\mu\text{mol}/\text{ml}$] derived from the 25 erythrocytes. To decrease the initial lactate concentration, the erythrocytes are washed five times with ten times their volume of physiological saline. This lowers the initial lactate concentration in the perfusion medium to 0.23 ± 0.02 S.E.M. (16) $\mu\text{mol}/\text{mol}$. 30 The medium is gassed with $\text{CO}_2 + \text{O}_2$ (5:95) during perfusion.

35 Into the perfusion of 150ml is added a sufficient quantity of two parenteral nutrient solutions, one containing 10 mM D-Fructose from a commercial source (5% Fructose in Electrolyte #75, Travenol, Facts and

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1 Comparison, August '83, p52b) and a new parenteral solution composition using glucose in place of fructose, a normal Na:Cl ratio, redox-balanced lactate, pyruvate and excess K as does Electrolyte #75. Glucose
5 enters the metabolic sequence at a "safe entry" point as herein defined. The composition of each solution is given in Table XVII below.

Sampling of Liver

For the analysis of liver, samples are rapidly frozen in vivo or during perfusion, by using the deep cooled clamps of Wollenberger, Ristau & Schoffa (1960). The resulting disc of liver tissue is ground to a fine powder in a cooled mortar with frequency additions of liquid N₂. The liver powder is transferred to a tared centrifuge tube cooled in liquid N₂ and 4 ml of ice-cold 6% (w/v) HClO₄ is then added to each gram of liver powder with constant stirring. The resulting slurry is allowed to thaw and then is homogenized in the centrifuge tube at a low speed with a glass pestle. The homogenate is kept ice-cold for 30 minutes, centrifuged, and the resulting supernatant is brought to pH 6-7 with 20% (w/v) KOH to precipitate the excess of HClO₄ as KClO₄. The assays are carried out on the clear supernatant.

Preparation of Liver Aldolase

25 Livers of large (300-450g) rats are bled by perfusion in situ with cold isoosmotic KCl and then homogenized with 4 vol. of KCl. After centrifugation at 30000 x g for 20 minutes, the supernatant is fractionated with (NH₄)₂SO₄ as described by Leuthardt & Wolfe (1955).
30 The final precipitate is taken up in a small volume of water (0.3 ml/g of original liver) and dialyzed against 200 vol. of water at 0C, changed every hour for 4h. The cloudy preparation is centrifuged and 0.1ml of 0.1 M EDTA is added to every 4ml of clear supernatant. Incubation for 1h at 25 °C completely inactivated sorbitol dehydrogenase (EC 1.1.1.14)

1

Table XVII
COMPOSITION OF FLUIDS

	UNITS	(1)	(2)	(3)
m moles/L				
5	Na	136 - 145	40	40
	K	3.5 - 5.0	35	35
	Ca	2.1 - 2.6		
	free $[Ca^{2+}]$	[1.06]		
	Mg	0.75 - 1.25		
10	free $[Mg^{2+}]$	[0.53]		
	meq Cations	142.7 - 153.2	75	75
	Cl	100 - 106	47.5	29
	HCO_3	26 - 28		26
	Pi	1 - 1.45	7.5	1.4
15	SO_4	0.32 - 0.94		
	l-lactate	0.6 - 1.8	20 (d,1)	15.64
	pyruvate			1.56
	Lact/Pyr		(inf.)	10
	d-Beta OH butyrate			
20	Acetoacetate			
	Beta HB/acac			
	Acetate			
	Others			
	meq anions	128.7 - 139.4	75	75
25	Na/Cl	1.28- 1.45	0.84	1.36
	Glucose	3.9 - 5.6		278
	Fructose		278	
	CO_2	0.99 - 1.39		1.5
	pH	7.35 - 7.45	-	7.4
30	m OsM	285 - 295	428	429.5

Footnotes for Table 1

(1) Indicates: Normal Human Plasma as reported in N.E.J.M. 283, 1285, (1970).

(2) Indicates: 5wt. % Fructose in Electrolyte #75 (commercially available from Travenol as shown in "Facts & Comparisons" Aug.'83, p.52b).

(3) Indicates 5% Glucose in Electrolyte Solution for parenteral nutrition from this patient following our outlines of safe entry points and a normalized Na/Cl ratio and redox state. Such a solution improves Solution 2 in this table.

1 (Hers, 1956), which would otherwise react with fructose. The final preparation, containing 35-45 mg of protein/ml, is stored at -18°C and is found to lose only about 30% activity in one year. In addition to aldolase activity, 5 it also contains glycerol 1-phosphate dehydrogenase (EC 1.1.1.8) activity and triose phosphate isomerase (EC 5.3.1.1) activity.

Other Aldolase Preparations

Chilled fresh rat and rabbit tissues are homogenized 10 with 14 vol. of 1 mM-EDTA and centrifuged for 20 minutes at 30000 x g. The supernatant obtained is used in assays without further purification. A crystalline preparation of rabbit muscle aldolase is supplied by the Boehringer Corp. (London) Ltd.

15 Analytical Methods

ATP is determined by the method described by Lamprecht & Trautschold (1963), ADP and AMP are determined in the combined assay of Adam (1963), Pi was determined by the method described by Berenblum & Chain (1938), 20 as modified by Martin & Doty (1949). Fructose 1-phosphate is determined by the method of Eggleston (1970). Fructose 1, 6-diphosphate, is measured together with total triose phosphates in the combined assay of Bucher & Hohorst (1963); pyruvate, phosphoenolpyruvate, 2- and 3- 25 phosphoglycerate are determined in sequence (Czok & Eckert, 1963). The references to other analytical methods are as follows: α -glycerophosphate (Hohorst, 1963b); L-(+)-lactate (Hohorst, 1963c); glucose 6-phosphate and fructose 6-phosphate (Hohorst, 1963c); glucose 1-phosphate 30 (Bermeyer & Klotzsch, 1963); glucose and fructose (Klotzsch & Bergmeyer, 1963); the sum of D-glyceraldehyde and glycerol (Pinter, Hayashi & Watson, 1967). For the 35 fluorimetric determination of very low concentrations of glyceraldehyde 3-phosphate and dihydroxyacetone phosphate by the method of Veech, Raijman, Dalziel & Krebs (1969),

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1 a portion of the neutralized supernatant is shaken for
1 minute with Florisil (100-200 U.S. mesh) to remove
flavins and then recentrifuged before use. In livers
perfused with fructose where the concentration of
5 dihydroxyacetone phosphate is increased, it is determined
by the spectrophotometric method of Bucher & Hohorst
(1963). IMP is determined by a combination of paper
chromatographic separation (Krebs & Hems, 1953) and a
spectrophotometric assay. A portion of deproteinized
10 liver extract (0.1 or 0.2ml) is dried onto a 1cm area on
Whatman no. 1 chromatograph paper under a current of hot
air. Duplicates, with and without added IMP standards
(10 μ l, 2mM solutions) on the same spot, are developed
by descending chromatography with the isobutyric acid-
15 ammonia solvent mixture described by Krebs & Hems (1953)
for 45-48h at room temperature. After drying in a
current of air, the papers are examined under u.v. light
from a Chromatolite lamp (Hanovia Ltd., Slough, Bucks,
U.K.) and absorbent areas are ringed by pencil. Average
20 distances run from the starting line are: IMP 23 cm,
ATP 27 cm, ADP 32, cm, AMP and inosine 37 cm. IMP areas,
and a blank area of similar size before the starting line,
are cut out and dropped into 4ml of 10mM potassium phos-
phate buffer, pH 7.0. After gentle mixing at intervals
25 for 1h, 3ml is removed and the extinction at 248nm in
1cm wide silica cells in a Zeiss spectrophotometer is
determined. At this wavelength, the E_{max} x
 10^3 for IMP is 12.3 (Deutsch, 1952). Recovery of
standards by the whole procedure is 93-104%.

30

RESULTS

The values of metabolites found in freeze clamped
liver are given in Table XVIII. Infusion of a fructose
solution at a rate sufficient to raise the blood fruc-
tose level to 10mM

35

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1

TABLE XVIII
Liver Contents of Metabolites
(After 10 Minutes of Perfusion)
Values Are In μ Moles/g Wet Weight

5

	(1)	(2)	(3)
D-Glucose	6.99	2.29	10
D-Fructose	about 0	10	about 0
Glucose 6-P	0.25	0.14	0.30
Fru-tose 1-P	0.23	8.72	0.25
10 Dihydroxyacetone -P	0.04	0.16	0.04
3 Phosphoglycerate	0.26	0.16	0.26
Lactate	0.79	1.34	0.79
Pyruvate	0.08	0.15	0.08

15

Footnotes for Table XVIII

- (1) Indicates liver before perfusion.
- (2) Indicates perfusion with solution 1 from commercial sources.
- (3) Indicates perfusion with solution 2 from this patient.

20

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1 drops liver and hence blood glucose level to 2.29mM
and raises fructose 1, P, over 35 fold to 8.7 umoles/g.
In contrast, using a glucose solution so as to raise the
blood level to 10 mM glucose has no appreciable
5 effects except for a small elevation of glucose 6-P.

In Table XIX, we see that raising blood
fructose causes a three fold drop in ATP and a seven
fold increase in IMP. The phosphate is simply stripped
off the nucleotides to put on fructose 1-P. In addition,
10 the inorganic Pi in liver drops from 4.2 to 1.7 umoles/g
weight. Taken together, this is a picture of profound
metabolic disorder in intracellular energy metabolism
which may be avoided by using the alternative NaCl bal-
anced, redox-balanced solution which uses nutrients of
15 the "safe entry point class".

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Table XIX

1 Liver Content of Nucleotides and Pi

5 Values are in umoles/g wet weight

	Control	Fructose Solution (1)	Glucose Solution (2)
ATP	2.22	0.51	2.22
ADP	0.78	0.66	0.78
AMP	0.26	0.20	0.26
10 IMP	0.165	1.14	0.165
Pi	4.25	1.67	4.25
metabolically active Pi	13.75	13.88	13.80

15

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1 In Table XX, we see the $[\text{NAD}^+]/[\text{NADH}]$ ratio
 calculated from the $[\text{l-lactate}]/[\text{pyruvate}]$ ratio or the
 $[\text{malate}]/[\text{oxaloacetate}]$ ratio increases with fructose
 by two fold. As predicted by the equation of the K_{G+G}
 reaction, this is accompanied by an incredible elevation
 of the free $[\Sigma \text{ATP}]/[\Sigma \text{ADP}][\Sigma \text{Pi}]$ ratio to $150,000 \text{M}^{-1}$,
 the highest values ever recorded. Whether near-
 equilibrium is reached in such an abnormal situation
 is not the point here. Rather, it is clear fructose
 abnormally decreases not only the total amounts of the
 adenine nucleotides (Table XIX) but also severely dis-
 torts their thermodynamic relationship thereby profoundly
 disordering the normal metabolic state of liver. In
 contrast, solution 2 has no effect, firstly because it
 15 does not violate the "safe entry point" concept, and also,
 because it has pH, redox and NaCl balance.

TABLE XX

Example 2: Using Class 1 Solutions for Parenteral Nutrition

Liver Nucleotide Ratios

	Control Liver	Perfused with Parenteral Nutrient (1)	Perfused with Parenteral Nutrient (2)
Free Cytoplasmic			
$\frac{[\text{NAD}^+]}{[\text{NADH}]}$	912	1812	912
Free Cytoplasmic*			
$\frac{[\Sigma \text{ATP}]}{[\Sigma \text{ADP}][\Sigma \text{Pi}]}$ M ⁻¹	11,517	151,000	11,517

30 *The free cytoplasmic $[\Sigma \text{ATP}]/[\Sigma \text{ADP}][\Sigma \text{Pi}]$ is calculated
 from equation 5 in this disclosure as described by Veech
 R. L., et al, J. Biol. Chem. 254, 6538-6547, 1979.

102

1 The example also illustrates the concept of "safe
entry points" discussed herein: Compounds which may be
included in solutions which directly contact living
cells, without, for instance, first passing through
5 the gut wall to be metabolically changed, constitute
the group herein identified by having "safe entry points".
Members of the "safe entry point group" where levels over
3mM may be used in fluids directly contacting cells
are:

10

l-Lactate
pyruvate

d B-Hydroxybutyrate
acetoacetate

D-Glucose

15

The upper limits to which even these may be used
depends upon the metabolite and medical situation and
no upper limit can be set absolutely without such
considerations. However, the sum of
20 lactate and pyruvate is generally in the level of 10-
12 mM in healthy, jogging adults. The sum of
betahydroxybutyrate and acetoacetate is in the range
5-7 mM/L plasma in healthy individuals undergoing
reducing three day fasts. (See Cahill G. F. and Aoki
25 T.T. in Cerebral Metabolism and Neural Function (1980)
Passonneau J.V., Hawkins R.A., Lust W.D. and Welsh F.A.
eds; pp 234-242, Williams & Wilkins, Baltimore).
Such levels may therefore be considered to be in a
"Normal" range and used safely in most normal condi-
30 tions excepting perhaps ketones in pregnant women
where the decision by the physician will depend upon
the medical necessity. (See Rudolf M.C.J. and
Sherwin R.S., Clinics in Endocr. & Metab. 12, pp 413-
428, 1983).

35

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1 The toxicity of elevating blood glucose above
13 mM/l is well documented in the studies of the
University Diabetes Group and must be balanced in
the physician's judgment by the need for calories in
5 the patient. Glucose is herein demonstrated, however,
to be much less toxic than fructose.

Compounds which may not be used parenterally as
"safe entry points" into the metabolic sequence,
as currently practiced in the art, are:

10

Acetate
Glycerol
Lactate (without pyruvate)
Pyruvate (without lactate)

15

Fructose

The methods used in this example are found in the
following reference: Woods HF, Eggleston LV, Krebs HA.
The cause of the accumulation of fructose 1-P on
fructose loading. Biochem J. 119: 501-510, 1970.

20

1 Example 44

Use of Class II Solutions for Peritoneal Dialysis
The procedure used here is similar to that
utilized by Klim and Williamson in Biochem. J. (1982)

5 214, 459-464

Materials

Male Wistar rats weighing 213+35g (66), at time
of death, are used: there are no significant
differences between the mean body weights of the
10 experimental groups. They are maintained on a standard
small animal diet, and water ad libitum in an animal
house with lights on from 08:00 to 20:00h. Chronic
uremia is induced by the five-sixths bilateral
nephrectomy technique (Morrison, 1966). Uremic rats
15 are allowed approximately 14 days to recover from the
last operation before use.

Peritoneal-Dialysis Solutions

A commercial peritoneal dialysis solution is used,
containing 45 mM acetate and 1.5% glucose (83mM) and
20 compared to a new dialysis solution of the present
invention (Example 3). The composition of the two
solutions is comparatively shown in Table XXI. Control
rats are simply given glucose to raise their blood
levels to those occurring in dialyzed animals.

25 The methods of measurement of liver metabolites
are those of Veech and are described amply in the
literature such as Veech et al. J. Biol. Chem. 254
6538-6547, 1979; Veech, Eggleston & Krebs Biochem. J.
30. 115, 609-619, 1969 and Veech et al. FEBS Letts.,
 117, K65-72, 1980.

1

TABLE XXI
Composition of Dialysis Fluids

	Units	Normal		Commercial	New
		m moles	Plasma	Fluid	Fluid
5	L Fluid		(1)	(2)	(3)
	Na	136 - 145		140	140
	K	3.5- 5.0		4	4
	Ca	2.1- 2.6		2.0	2.0
	free $[Ca^{2+}]$	[1.06]			
10	Mg	0.75- 1.25		0.75	0.75
	Sigma mEq. Cations	142.7 - 153.2		150	150
	Cl	100 - 106		105	105
	HCO_3	26 - 28			29
	Sigma Pi	1 - 1.45			
15	SO_4	0.32- 0.94			
	L-lactate	0.6 - 1.8			8.21
	pyruvate				1.79
	Lact/pyr				4.6
	D-Beta-OH butyrate				3.24
20	Acetoacetate				2.76
	BetaHB/acac				1.17
	Acetate		45		
	Sigma mEq anions	128.7 - 139.4		150	150
	Na/Cl	1.28- 1.45		1.33	1.33
25	Glucose	3.9 - 5.6		83	83
	CO_2	0.99- 1.39			1.5
	pH	7.35- 7.45		5.5-6.5	7.4
	Sigma m Osm	285 - 295		379.75	379.75

30 Footnotes for Table 1

(1) indicates: Normal plasma N.E.J.M. 283, 1285, 1970.

(2) indicates: Commercial Fluid-Peritoneal dialysis with 1.5% Glucose. American McGaw, Facts and

35 Comparisons, October 1982, page 704.

1 (3) indicates: New fluid-improved peritoneal
dialysis fluid formulated in this disclosure is meant to
mimic the ideal commercial fluid. This new fluid is not
to be taken as "ideal" but is simply a way of illustrating
5 why acetate should not be used. A better fluid would
also contain HCO_3/CO_2 , Lactate/pyr & Beta-HB-/AcAc
but would have an increased Na:Cl ratio of between
1.38 to 1.41 to increase alkali reserve in the chronically
acidotic uremics. Cl^- could be 100, HCO_3^- of 34 with
10 $[\text{CO}_2]$ of 1.7mM as an example of a fluid designed in
conformity with the principles outlined herein. Such
fluids have 1) redox balance and hence normal phosphoryla-
tion state achieved with 2) pair of ratioed couples so as
to achieve a normal M desired NaCl ratio 3) while causing
15 less pathological consequences than present art allows.

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1 The values of metabolites in rat liver are given
 after seventy minutes of peritoneal dialysis in
 Table XXII.

(Electrolyte 14)

5 Table XXII

	Control	(1)	(2)
		Acetate	Redox-Balanced
		Peritoneal	Dialysis
		Dialysis	Fluid
10 N	(13)	(10)	(10)
	Values are given in n moles/g wet weight liver.		
Dihydroxy-	46	53	69
acetone P	+_-3	+_-5	
15 3-Phospho-	294	405	294
glycerate	+_-15	+_-27	
l-Lactate	727	743	6081
	+_-36	+_-70	
20 Pyruvate	158	98	1326
	+_-13	+_-9	
d-Beta Hydroxy-	117	151	2400
25 butyrate	+_-20	+_-12	
Acetoacetate	100	117	1380
	+_-19	+_-8	
30 Acetate	20	33000	20

In Table XXIII are given the changes in liver content of divalent cations, Pi, PPi and total metabolizable phosphate containing compounds after such treatment.

1 TABLE XXIII
 Changes in Mg, Ca, Pi and PPi Content in Rat Liver During
 Dialysis

5 Values in umoles/g wet weight liver.

		(1)		(2)	
		Acetate Dialysis	Change Induced by Acetate	New Dialysis	Change Induced by new Dialysis
	Control				
10		(16)	(16)		
	Ca	1.06	1.76 +.70	1.06	0
	Mg	11.76	12.94 +1.18	11.8	0
	Inorganic Pyrophosphate (PPi)	.018	0.198 +0.18	0.018	0
15	Sigma Adenine				
	Nucleotides	7.95	9.43 +1.48	7.95	0
	Sigma Guanine				
	Nucleotides	1.56	1.97 +0.41	1.56	0
	Sigma Glycolytic				
20	Pi	0.65	1.65 +0.06	0.85	+.2
	Sigma Metabolic				
	Pi	13.75	17.97 +4.22	13.95	+.2
	from all measured				
25	Metabolites				

It should be remembered that normal hemodialysis with 35 mM acetate makes the abnormal elevation in PPi reach 100 times normal with a quadrupling of liver Ca at the expense of bone stores of calcium. It is thus exaggerated in every way. Solutions containing 35mM Na Acetate currently account for about of 80% of hemodialysis in the U.S. The increased Pi demonstrated herein during acetate dialysis is "hidden" in liver and flows out (into blood) after dialysis accounting for why such patients remain persistently hyperphosphatemic leading to much current pathology found in chronic dialysis patients.

1 The data presented in Table XXIII clearly show
that peritoneal dialysis, with acetate containing
fluids, leads to gross elevations of liver inorganic
pyrophosphate and liver calcium. While not widely
5 appreciated, inorganic pyrophosphate (PPi) is an impor-
tant controller of cellular metabolic pathways of many
types. See Lawson J.W.R. et al. in Gluconeogenesis,
1976 (Hanson R.W. & Mehlman M.A. Eds) pp 481-511, John
Wiley & Sons, New York). Changes in PPi are therefore
10 likely to be of widespread significance. The 70%
increase in liver calcium is, of course, clearly large
and of potential significance because of the importance
calcium plays as an activator of many intracellular
protein kinases.

15 Finally, Table XXIII shows that acetate induces
a rapid increase of 4.2 umoles/g wet weight of the
liver's rapidly metabolizing phosphate compounds. It
derives this excess Σ Pi from the blood and other phos-
phate stores. When the acetate is finally metabolized,
20 this phosphate returns to the blood where Pi is 1-1.45mM.
Since liver and blood are roughly equal in weight in
the normal adult, this movement of Σ Pi out of liver
must inevitably lead to the hyperphosphatemia which
is a major and persistent pathological sequela of uremia
25 treated by current dialysis practice. This persistent
elevation of blood Pi leads to chronic hyperparathyroidism,
hypocalcemia, accelerated bone disease, ectopic calci-
fication of tissue and many other causes of morbidity
and even mortality in chronic renal disease. Because
30 the phosphate accumulates in the liver during acetate
dialysis, it is effectively "hidden" from the beneficial
effects which dialysis is trying to obtain, namely the
removal of excess dietary Σ Pi which is taken in by the
patient during the intradialysis periods.

110

1

(Electrolyte-14)

TABLE XXIV

Table XXIV gives the results obtained for the redox and phosphorylation states calculated, as described in Equations 4 and 5. Values are given as means + S.E.M.

		(1)	(2)
	Control	Acetate Dialysis	New Dialysis
	(5)	(6)	(6)
10 N			
Cytoplasmic free			
<u>[NAD⁺]</u>	1944	1209*	about 1944
<u>[NADH]</u>	+ 94	+ 88	
Mitochondrial free			
<u>[NAD⁺]</u>	18.2	17.4	about 18.2
<u>[NADH]</u>	+2.3	+2.6	
cytoplasmic			
<u>[Σ ATP] M⁻¹</u>	25,800	13,700*	about 25,800
<u>[Σ ADP] [Σ Pi]</u>	+ 3,200	+ 2,600	

15 *indicates significant difference at P > 0.05.
20

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1 The use of acetate in a peritoneal dialysis
fluid obviously causes a significant decrease in the
free cytoplasmic $[NAD^+]/[NADH]$ and an even more profound
decrease in the cytoplasmic $[\Sigma ATP]/[\Sigma ADP][\Sigma Pi]$ ratio.
5 This is so because the free $[NAD^+]/[NADH]$ ratio of cyto-
plasm is directly linked to the free cytoplasmic
 $[\Sigma ATP]/[\Sigma ADP][\Sigma Pi]$ by equation 5. (See Veech, et al.
J. Biol. Chem. 254, 6538-6547, 1979). On page 704 of
Facts and Comparisons, October, 1982, are listed 16
10 peritoneal dialysis solutions, using 35 to 45 mMolar
(d,l)-lactate in commercial peritoneal dialysis solutions
made by four different commercial manufacturers. These
solutions, in addition to the 7 commercial acetates
containing peritoneal dialysis solutions, make up the
15 current state of the art. None achieve the normal
Na/Cl ratio they desire in the manner described herein.

20 No example of the effects of using 35 to 45 mM L-
lactate alone, in a peritoneal dialysis solution, need
be given. It is by now obvious, from the teachings
here presented, that such solutions are entirely without
redox balance but indeed induce a profound lactic acidosis
with a pathological decrease in the free cytoplasmic
 $[NAD^+]/[NADH]$ and the free cytoplasmic $[ATP]/[ADP][Pi]$
to which it is linked by equation 5. It is also obvious
25 that redox-balanced solutions, made by the principles
outlined here, would be an advance in the present art.

1

Example 45

Hemodialysis

Using hemodialysis equipment, which is the current major type in use, (see Keshaviah et al., CRC Critical Reviews in Biomedical Engineering 9, 201-244, 1983) and using the most common type of dialysis fluid currently in use in the art, which uses between 35 to 45 mMoles/L of Na acetate to correct the anion gap, (see Parsons F.M. & Stewart W.K., The Composition of Dialysis Fluid in Replacement of Renal Function by Dialysis, 2nd edition (1983) (Drukker W., Parsons F.M. & Maher J.F., eds) pp 148-170, (Martinus, Nijhoff, Hingham) we may obviously predict the effects, upon body organs such as the liver, of such treatment.

15 Methods

Rats are made uremic as described in the previous example. After five days, they are fasted, attached to a miniature hemodialysis apparatus, heparinized and dialyzed with two different solutions, one representing the most common types of currently used hemodialysis solutions, and another where the anion gap is made up without the use of $\text{HCO}_3^-/\text{CO}_2$, but instead, with the use of L-lactate/pyruvate and D-B-Hydroxybutyrate/acetooacetate as are given in the class 2-a solutions in this disclosure, as for example 2-a-8, Redox-Balanced Ringers. It should be understood that I do not conclude such a solution as 2-a-8 is the best solution for such a purpose, but I shall show it is superior to the existing art and may be used in the bulk of existing apparatus which contain deaerators* and currently use acetate containing hemodialysis fluids. (Keshaviah et al. CRC Critical Reviews in Biomedical Engineering 9, 201-244, 1983). A few current machine, typically 1 out of 10 in the dialysis centers I have surveyed have dialysis machines of the type described by

1 Miller J.H. et al. Trans Am Soc artif Internal Organs 25,
404-408, 1979. Such machines can use HCO_3^- containing
solutions. Such $\text{HCO}_3^-/\text{CO}_2$ solutions are preferred.

5 The compositions of the two example solutions
are given in Table XXV.

Example 4 Table XIV Solution for Hemodialysis of a Uremic Rat.

Units	Normal	(1)		(2)	
		Plasma	Usual	Redox-Balanced	Hemodialysis Solution
anoles ----- L fluid	N.E.J.M. 283, 1285 1970	145	130-135	130	
Na		136 - 145	130-135	130	
K		3.5 - 5.0	0 - 1.5	4	
Ca free [Ca ²⁺] [1.06]		2.1 - 2.6	1.25	1.5	
Mg free [Mg ²⁺] [0.53]		0.75 - 1.25	0.5	-	
Z Eq Cations	142.7-153.2	133.5-140	137		
Cl	100 - 106	100.5	96		
HCO ₃		26 - 28			
Σ Pi		1 - 1.45			
SO ₄		0.32 - 0.94			
L - lactate	0.6 - 1.0		32.1		
pyruvate			1.9		
Lact/pyr			17		

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D 6.0Hbutyrate	5
acetoacetate	2
B Hb/ acac	2.5
acetate	33.5±40
Other	
Σ Eq anions	128.7-139.4
Eq anions	133.5±140
Ia/Cl	1.28 - 1.45
	1.29-1.34
Glucose	3.9 - 5.6
or others	0-101
CO ₂	0.99 - 1.39
	0
pH	7.35 - 7.45
	~6.5
Σ osm	285 - 295
	270.25 to
	375
	272.5

(1) The composition of the usual hemodialysis solution is taken from Parsons and Stewart, 1983, cited above.

(2) Composition of solution 2-a-B is taken from this application except that the lactate/riboflavine ratio is decreased to 17 to accomodate the absence of glucose since most current hemodialysis fluids use Acetate without glucose. This composition is chosen to compare with current acetate hemodialysis practice. This solution should not be taken as "ideal" or even as recommended, but rather illustrative.

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1 The rats are dialyzed with solutions 1 and 2
for four hours; the animals are sacrificed and the livers
freeze clamped. A group of normal rats, starved 48 hours,
are also sacrificed and their livers freeze clamped
5 to serve as controls. Metabolites are measured, as
previously described.

10 In Table XXVI, we see that both acetate and new
redox-balanced dialysis fluids elevate liver sugar and
the first portion of the gluconeogenic pathway. During
acetate dialysis, changes occur throughout the glucone-
ogenic sequence and the ratio of one metabolite to
another changes.

15

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1 Table XXVI Liver Metabolites from Rats Dialysed with Acetate
 Dialysis Fluid versus New Redox-Balanced Dialysis
 Fluids without $\text{HCO}_3^-/\text{CO}_2$
 Values are given as means + S.E.M. in nmoles/g wet
 5 weight. A * indicates a significant difference
 from normal rats at $P < 0.05$ as judged by Student's T
 Test.

		Untreated Starved Rats	Commercial Acetate Dialysis	New Redox-Balanced Dialysis
10	N	13	10	7.2*
	$10^{-3} \times \text{glucose}$	4.81+0.21	7.94+0.42	88.5*
	glucose 6-P	59+2	99*+10	10.5*
	glucose 1-P	7+1	11*+1	25.2*
	fructose 6-P	17+1	32*+3	6.9
15	fructose 1,6 bis-P	4.6+0.4	23*+6	16.5
	DHAP	11+1	36*+4	234
	3-phosphoglycerate	156+14	581*+62	110
	PEP	73+5	330*+40	1260*
	pyruvate	10+1	27*+6	21300*
20	L-lactate	171+17	721+208	402
	L-malate	268+28	592*+84	177
	α -ketoglutarate	118+13	86+17	25.5
	isocitrate	17+2	41*+3	462
	citrate	308+42	944*+85	1330*
25	acetoacetate	638+33	643+66	3300*
	D-B OHbutyrate	1643+75	983*+83	350
	UDP-glucose	350+15	367+25	205
	UTP	205+9	186+8	20
	acetate	20	25000	

30

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1 In Table XXVII are presented the changes in the
 controlling co-factor ratios after the two types of
 dialysis.

TABLE XXVII

5 Free Nucleotide Ratios in Freeze Clamped Rat Liver After
Acetate and Redox-Balanced Hemodialysis

Values are given as mean + S.E.M. An * indicates
 a significant difference from control values of
 $P < 0.02$ as judged.

		Starved	Acetate	Redox-Balanced
		Control	Dialysis	Dialysis
	(n)	(13)	(10)	
10	Cytoplasmic $\frac{[NAD^+]}{[NADH]}$	587 + 86	391 + 35	587
15	$10^3 \frac{x}{[NADPH]}$	7.3 + .7	2.1* + .3	7.3
20	$\frac{[\Sigma ATP]}{[\Sigma ADP][\Sigma Pi]M}^{-1}$	3710 + 580	2090 + 280	3710
	mitochondrial $\frac{[NAD^+]}{[NADH]}$	8.1 + 0.7	13.8* + 1.4	8.1

25 In Table XXVII we see that acetate dialysis causes
 oxidation of the mitochondrial $[NAD^+]/[NADH]$ ratio and
 reduction of the free cytoplasmic $[NADP^+]/[NADPH]$ ratio
 while redox-balanced dialysis causes no change as judged
 by the isocitrate/ α -ketoglutarate ratio.

30

35

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1 In Table XXVIII are presented the results of
 the measurement of the Ca, Mg, phosphate and pyro-
 phosphate content of rat liver after acetate versus redox-
 balanced hemodialysis.

5

TABLE XXVIII
Changes in Mg, Ca and Phosphate Compounds in
Liver Following Acetate versus Redox-Balanced
Hemodialysis.

		Acetate	Redox-Balanced
	Control	Hemodialysis	Hemodialysis
10	n	13	10
Ca		1.33	+2.89
Mg		10.1	+1.8
PPi		0.024	+2.00
15	Pi	4.22	+3.73
	Σ Adenine Nucleotide		
	Pi	9.32	+0.07
	Σ Guanine Nucleotide		
	Pi	1.76	+0.19
20	Σ Glycolytic Pi	0.36	+0.86
	Σ Pi Increased from		+.50
	All measured		
	metabolites	15.71	+8.85
			+.50

25 We see in Table XXVIII that acetate dialysis
 raises inorganic pyrophosphate 200 times while redox-
 balanced dialysis makes no change. Acetate hemodialysis
 increases liver calcium three fold; redox-balanced
 dialysis makes no change. Acetate hemodialysis increases
 30 total liver metabolizable phosphate by 8.8 m moles/g,
 while redox-balanced dialysis increases liver
 metabolizable phosphate by only 0.5 m moles/g, or 16 times.
 The "hidden" phosphate, inaccessible to dialysis after
 acetate hemodialysis, is the largest ever seen. The
 35 metabolic pathology is therefore even greater than that
 in Example 44.

Example 45

1 Solutions of this invention when administered not only regulate redox state and phosphorylation, but also further tend to normalize the following states:

5 (1) Distribution of water between intracellular and extracellular fluid.

(2) Distribution of the inorganic electrolytes Na^+ , K^+ , Cl^- and Ca^{2+} between intracellular and extracellular fluid, and

10 (3) Transmembrane cellular potential. ΔE

The following equations state the governing scientific laws involved:

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0. Eqn 0 - The Second Law

J. Willard Gibbs. On the equilibrium of heterogeneous substances. *J. Conn Acad Sci* 1876; III : 343.

0 - 1 Definition of Gibbs Free Energy and Other Properties of State:

$$G = H - TS$$

where:

- G ~ Gibbs free energy
- H ~ Enthalpy or heat content
- T ~ absolute temperature
- S ~ Entropy, or state of randomness or disorder

0 - 1 a Entropy may be more rigorously defined by statistical and quantum mechanics in the Boltzmann Equation:

$$S = k_B \ln \Omega$$

where:

- S ~ Entropy
- k_B ~ Boltzmann constant = R (gas constant)
Avagadro's number

$$\Omega \sim \text{Degeneracy} = 1.38 \times 10^{-23} J/\Omega_K$$

0 - 2

$$\Delta G = \Delta H - T \Delta S$$

where ~ change in

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0 - 3 Standard Free Energy ~ ΔG°

$$\Delta G = \Delta G^{\circ} + RT \ln \frac{[Products]}{[Reactants]}$$

where:

$$R \sim \text{gas constant} \\ = 1.987 \text{ calories}/\text{mole}$$

$$T = \text{and } R_K \sim 273 + {}^{\circ}C$$

$$\ln \sim 2.303 \log_{10}$$

$$\Delta G^{\circ} = -RT \ln K_{eq}$$

$$\text{where: } K_{eq} \sim \frac{[Products]}{[Reactants]}$$

0 - 4 At equilibrium, $\Delta G = 0$, so in $A + B \leftrightarrow C + D$

$$\Delta G = -RT \ln K_{eq} + RT \ln \frac{[C][D]}{[A][B]}$$

where:
 $[] \sim \text{activity or } \sim \text{concentration}$

"A theory is the more impressive the greater the simplicity of its premises, the more different are the kinds of things it relates, and the more extended is its range of applicability... It is the only physical theory of universal content which I am convinced, that within the framework of applicability of its basic concepts, will never be overthrown.

A. Einstein

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1 I

Eqn 1 - The Henderson-Hasselbalch Equation

The major buffer and controller of extra and intracellular pH.

Henderson LH. Blood, A Study in General Physiology.

5

Silliman Lectures, Yale University Press, 1928

1.a

$$\text{pH} = \text{pK}_a + \log \frac{[\text{HCO}_3^-]}{[\text{CO}_2]}$$

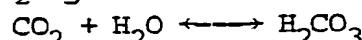
where:

10

pK_a = 6.10 at 38°C and serum concentrations of electrolytes

1.b

The solubility of CO_2 in fluid, i.e. dissolved CO_2 gas plus H_2CO_3 from:



15

$$[\text{CO}_2] \text{ in mmol/liter} = \frac{\text{pCO}_2 \text{ in mmHg}}{760 \text{ mmHg}} \cdot \frac{\text{cmol CO}_2/\text{ml of H}_2\text{O}}{22.26 \text{ L/mole}} \cdot \frac{1000 \text{ mmol}}{\text{mole}}$$

α_{CO_2} = 0.553/ml serum H_2O at 38°C from:

Van Slyke DD. J Biol Chem 73: 765-799, 1928

20 1.c

The pH of a bicarbonate containing solution to which has been added a carboxylic acid such as acetic, lactic, acetoacetic acid with a pK' in the 3 to 4 range and where the concentration of HCO_3^- is much larger than the concentration of carboxylic acid:

25

$$\text{pH} = \text{pK}_a + \log \left\{ \frac{[\text{HCO}_3^-]}{2([\text{HCO}_3^-] - [\text{HA}])} \right\} - \frac{1}{2}$$

Thus adding 1.8 mM Hlactate and 0.2 mM Hpyruvate to 25 mM NaHCO_3 yeids what pH?

30

$$\begin{aligned} \text{pH} &= \text{pK}_a + \log \left\{ \frac{[25]}{2([\text{HCO}_3^-] - [\text{HA}])} \right\} - \frac{1}{2} \\ &= 6.1 - (1.36) \\ &= 7.46 \end{aligned}$$

35

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11 Donnan Equilibrium Equation

Donnan FG. *J Electrochem* 17: 572, 1911.
Donnan FG. *Chem Rev* 1: 73-90, 1924.

1. From Gibbs (Eqn 0)

$$RT \ln \frac{[Cl^-]_1}{[Cl^-]_2} + RT \ln \frac{[Na^+]_1}{[Na^+]_2}$$

二

$$1. a \quad \frac{[Cl^-]_1}{[Cl^-]_2} = \frac{[Na^+]_1}{[Na^+]_2}$$

$$\text{Therefore: } \frac{[Cl^-]_1}{[Cl^-]_2} = \frac{[Cl^-]_2}{[Cl^-]_1 + z[A^{z-}]_1} = \frac{[Na^+]_2}{[Na^+]_1}$$

and for polyvalents:

$$\frac{[\text{Anions}]_1}{[\text{Anions}]_2} = \frac{[\text{Cations}]_1}{[\text{Cations}]_2}$$

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2. From the Law of Electrically Neutrality:

$$\begin{aligned} [\text{Na}^+]_2 &= [\text{Cl}^-]_2 \\ [\text{Na}^+]_1 &= [\text{Cl}^-]_1 + z [\text{A}^{z-}]_1 \end{aligned}$$

3. Quadratic equation:

$$x = \frac{-b \pm \sqrt{b^2 - 4ac}}{2a}$$

Example: Consider albumin dialysed against 100% CO_2 / 3.13 NaHCO_3 buffer with 1.17 M albumin (i.e. 8% solution). Hypothetically keep charge on albumin at -20/mole.

$$\begin{aligned} \frac{[\text{HCO}_3^-]_i}{[\text{HCO}_3^-]_0} &= \frac{[\text{HCO}_3^-]_0}{[\text{HCO}_3^-]_i + 20[\text{Alb}^{-20}]} = \frac{[\text{Na}^+]_0}{[\text{Na}^+]_i} \\ \frac{[\text{HCO}_3^-]_i}{3.13 \times 10^{-3}} &= \frac{[\text{HCO}_3^-]_0}{3.13 \times 10^{-3}} \\ [\text{HCO}_3^-]_i &= 0.4 \times 10^{-3} \text{M} \end{aligned}$$

II Eqn 2 Multicomponent Donnan Equilibrium System for Solutions Such as the Hemodialysis of Blood Plasma Electrolytes:

where $\Delta p = 0$ and all components but albumin are permanent. Subscript 0 = in dialysis fluid, subscript i = in patient's plasma, Δp = difference in pressure.

2.a.

$$\frac{[\text{Na}^+]}{[\text{Na}^+]} = \frac{[\text{K}^+]}{[\text{K}^+]} = \frac{[\text{Ca}^{2+}]}{[\text{Ca}^{2+}]} = \frac{[\text{Mg}^{2+}]}{[\text{Mg}^{2+}]} = \frac{[\text{Cl}^-]}{[\text{Cl}^-]} = \frac{[\text{HCO}_3^-]}{[\text{HCO}_3^-]} = \frac{[\text{Pi}]}{[\text{Pi}]} = \frac{[\text{Pyr}]}{[\text{Pyr}]} = \frac{[\text{Lac}^-]}{[\text{Lac}^-]} = \frac{[\text{BHB}^-]}{[\text{BHB}^-]} = \frac{[\text{acet}^-]}{[\text{acet}^-]} = \frac{[\text{BHB}^-]}{[\text{BHB}^-]} = \frac{[\text{acet}^-]}{[\text{acet}^-]}_0$$

$$\frac{[\text{Na}^+]}{[\text{Na}^+]} = \frac{[\text{K}^+]}{[\text{K}^+]} = \frac{[\text{Ca}^{2+}]}{[\text{Ca}^{2+}]} = \frac{[\text{Mg}^{2+}]}{[\text{Mg}^{2+}]} = \frac{[\text{Cl}^-]}{[\text{Cl}^-]} = \frac{[\text{HCO}_3^-]}{[\text{HCO}_3^-]} = \frac{[\text{Pi}]}{[\text{Pi}]} = \frac{[\text{Pyr}]}{[\text{Pyr}]} = \frac{[\text{Lac}^-]}{[\text{Lac}^-]} = \frac{[\text{BHB}^-]}{[\text{BHB}^-]} = \frac{[\text{acet}^-]}{[\text{acet}^-]}_0$$

Statement of electrical neutrality on two sides of an uncharged membrane

2.b.1.

$$[\text{Na}^+]_0 + [\text{K}^+]_0 + 2[\text{Ca}^{2+}]_0 + 2[\text{Mg}^{2+}]_0 = [\text{Cl}^-]_0 + [\text{HCO}_3^-]_0 + 1.81 \text{Pi}^{-1.8} + [\text{Lac}^-]_0 + [\text{Pyr}^-]_0 + [\text{acet}^-]_0 + [\text{BHB}^-]_0 + [\text{acet}^-]_0$$

2.b.2.

$$[\text{Na}^+]_i + [\text{K}^+]_i + 2[\text{Ca}^{2+}]_i + 2[\text{Mg}^{2+}]_i = [\text{Cl}^-]_i + [\text{HCO}_3^-]_i + 1.81 \text{Pi}^{-1.8} + [\text{Lac}^-]_i + [\text{Pyr}^-]_i + [\text{acet}^-]_i + [\text{BHB}^-]_i + [\text{acet}^-]_i + 2[\text{prot}^+]_i$$

Distribution of cations on two sides of the membrane:

2.c.

$$[\text{K}^+]_i = [\text{K}^+]_0 \frac{[\text{Na}^+]}{[\text{Na}^+]_0} ; \quad [\text{Ca}^{2+}]_i = [\text{Ca}^{2+}]_0 \frac{[\text{Na}^+]}{[\text{Na}^+]_0}^2 ; \quad [\text{Mg}^{2+}]_i = [\text{Mg}^{2+}]_0 \frac{[\text{Na}^+]}{[\text{Na}^+]_0}^2$$

Distribution of Anions:

123a

2.4

$$\begin{aligned}
 [Cl^-]_i &= \frac{[Na^+]}{[Na^+]_0} [Cl^-]_0; \quad [HCO_3^-]_i = \frac{[Na^+]}{[Na^+]_0} [HCO_3^-]_0; \quad [acet^-]_i = \frac{[Na^+]}{[Na^+]_0} [acet^-]_0; \quad [Pi]_i = \frac{[Na^+]}{[Na^+]_0} [Pi]_0; \\
 [lac^-]_i &= \frac{[Na^+]}{[Na^+]_0} [lac^-]_0; \quad [pyr^-]_i = \frac{[Na^+]}{[Na^+]_0} [pyr^-]_0; \quad [lact^-]_i = \frac{[Na^+]}{[Na^+]_0} [lact^-]_0; \quad [BHB^-]_i = \frac{[Na^+]}{[Na^+]_0} [BHB^-]_0
 \end{aligned}$$

Now solving for $[Na^+]_i / [Na^+]_0$ for a dialysis fluid₀ of known composition:

2.5

$$\begin{aligned}
 \frac{[Na^+]}{[Na^+]_0} [Na^+]_0 + [K^+]_0 + \frac{2[Na^+]}{[Na^+]_0} [Ca^{2+}]_0 + [Mg^{2+}]_0 &= \\
 \frac{[Na^+]}{[Na^+]_0} [Cl^-]_0 + [HCO_3^-]_0 + [acet^-]_0 + [lact^-]_0 + [pyr^-]_0 + [lact^-]_0 + [BHB^-]_0 + 1.0 \frac{[Na^+]}{[Na^+]_0} [Pi]_0 + \frac{[Na^+]}{[Na^+]_0} [prot^-]_0
 \end{aligned}$$

and:

$$\frac{2.4}{\frac{[Na^+]_0 + [K^+]_0 + 2[Ca^{2+}]_0 + [Mg^{2+}]_0}{[Na^+]_0^2 + \dots + [Na^+]_i^2 - 1.0 [Na^+]_i - 1.0 [Pi]_0 [Na^+]_0 + 0.8 [Na^+]_i (-0.8) [Na^+]_0} [Na^+]_i^3} [Na^+]_0^2$$

$$[Cl^-]_0 + [HCO_3^-]_0 + [acet^-]_0 + [lact^-]_0 + [pyr^-]_0 + [lact^-]_0 + [BHB^-]_0$$

Plasma [concentration] • 0.935 x plasma H_2O [concentration]

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1 III

Eqn 3. Nernst Equation - ΔE

Nernst W. Theoretical Chemistry 4th Edition, 1904,
 MacMillan, London. See also Silliam Lecture, 1906, Yale
 U. Press, New Haven.

5

$$3. \Delta E = - \frac{RT}{nF} \ln \frac{[\text{anion}^-]_{\text{outside}}}{[\text{anion}^-]_{\text{inside}}}$$

or:

10

$$\Delta E = - \frac{RT}{nF} \ln \frac{[\text{cation}^+]_{\text{inside}}}{[\text{cation}^+]_{\text{outside}}}$$

where:

at 38°C T ~ 311 °K

R, the gas constant ~ 8.314 hiykes/degree/mole

15

n ~ number of equivalents

F, the Faraday, ~ 96,494 coulombs

 ΔE ~ potential in voltsTo convert \ln to \log_{10} , multiply by 2.303

20

From Cornell N, Anal Biochem 1980; 102: 326-331, for
 isolated hepatocytes from starved rats incubated in Krebs-
 Henseleit.

[0.128 M Cl⁻] outside

$$\Delta E = -0.0617 \log \frac{[0.128 \text{ M Cl}^-]_{\text{outside}}}{[0.041 \text{ M Cl}^-]_{\text{inside}}}$$

25

$$\Delta E = -0.0305 \text{ V or } -30.5 \text{ mV}$$

and for cat brain, from Eccles JC. The Physiology of Nerve Cell, 1957, Johns Hopkins U Press, Baltimore.

[0.125 M Cl⁻] outside

$$\Delta E = -0.0617 \log \frac{[0.125 \text{ M Cl}^-]_{\text{outside}}}{[0.009 \text{ M Cl}^-]_{\text{inside}}}$$

30

$$\Delta E = -0.0705 \text{ V or } -70.5 \text{ mV}$$

3.b Redox Potential of Half Reactions

RT [oxidized]

$$E_h = E^{\circ} + \frac{RT}{nF} \ln \frac{[\text{oxidized}]}{[\text{reduced}]}$$

35

where:

R ~ 8.31431 J/°K/mole

T ~ 0 °K

n ~ number of electrons

F ~ Faraday ~ 96,494 coulombs

ln ~ 2.03 log₁₀

125

IV Eqn 4 Redox State Equations. $[NAD^+] / [NADH]$ or $[NADP^+] / [NADPH]$.

Near equilibrium reactions are given a number depending upon location. The E^0 of the $[NAD^+]/[NADH]$ couple at pH 7 is -0.32V. That of the $[NADP^+]/[NADPH]$ couple, -0.35 V.

Abbreviation	Definition of K_{eq}	Value of K_{eq} at pH 0	Value of K_{eq} at pH 7.0	Value of E^0 at pH 7.0
Enzyme No.	$K_{eq} = \frac{[E]_0}{[E]_0 + [E]_{eq}}$	$K_{eq} = 0$	K_{eq} at pH 7 at pH 7.0	E^0 at pH 7.0
			<u>oxidized</u>	<u>reduced</u>
			$CO_2 = 1.5 \text{ mM}$	0.5 mM NH_4^+
				1 mM Pi^-

Cytoplasmic NAD - linked Dehydrogenases

4 c 1	K_{LDH}	$\frac{[\text{pyruvate}^{-}][\text{NADH}][\text{H}^{+}]}{[\text{L-lactate}][\text{NAD}^{+}]}$	$1.11 \times 10^{-11} \text{ M}$	1.11×10^{-4}	-0.201
EC 1.1.1.27					
4 c 2	K_{MDH}	$\frac{[\text{oxaloacetate}^{2-}][\text{NADH}][\text{H}^{+}]}{[\text{1}-\text{oxalate}][\text{NAD}^{+}]}$	$2.86 \times 10^{-12} \text{ M}$	2.86×10^{-5}	-0.184
EC 1.1.1.37					
4 c 3	K_{6PDH}	$\frac{[\alpha\text{-glycerol-P}^{2-}][\text{NADH}][\text{H}^{+}]}{[\text{DHAP2-}][\text{NAD}^{+}]}$	$1.3 \times 10^{-11} \text{ M}$	1.3×10^{-4}	-0.263
EC 1.1.1.94					
4 c 4	K_{GAFDH}	$\frac{[1,3\text{-DGP}^{4-}][\text{NADH}][\text{H}^{+}]}{[\text{GAP2-}][\text{Pi}^{2-}][\text{NAD}^{+}]}$	$5.3 \times 10^{-8} \text{ M}$	5.3×10^{-1}	-0.302
EC 1.2.1.12					
4 c 5	K_{ADH}	$\frac{[\text{acetaldehyde}][\text{NADH}][\text{H}^{+}]}{[\text{ethanol}][\text{NAD}^{+}]}$	$1.94 \times 10^{-11} \text{ M}$	1.9×10^{-4}	-0.209
EC 1.1.1.1					
	$K_{1,3DH}$	$\frac{[\text{d-fructose}][\text{NADH}][\text{H}^{+}]}{[\text{d-sorbitol}][\text{NAD}^{+}]}$	$1.14 \times 10^{-9} \text{ M}$	1.14×10^{-2}	-0.252
EC 1.1.1.14					

EXCERPT OF SUBSTITUTE SHEET

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Mitochondrial NAD - Linked Dehydrogenases

$$\begin{aligned}
 4 \bullet 1 \quad K_{\text{NBDH}} &= \frac{[\text{acetacetate}^-\text{][NADH}^+\text{H}^+]}{[\text{d-}\beta\text{-hydroxybutyrate}^-\text{][NAD}^+]} \quad 4.93 \times 10^{-9} \text{ M} \quad 4.93 \times 10^{-2} \quad -0.261 \\
 \text{EC 1.1.1.30} \quad & \\
 4 \bullet 2 \quad K_{\text{GIDH}} &= \frac{[\text{fum-}\text{KG}^2-\text{][NADH}^+\text{H}^+]}{[\text{fum-}\text{KG}^2-\text{][NADH}^+\text{H}^+]} \quad 3.87 \times 10^{-13} \text{ M}^2 \quad 3.87 \times 10^{-6} \text{ M} \quad -0.158 \quad -0.257 \\
 \text{EC 1.1.1.31} \quad & \\
 4 \bullet 3 \quad K_{\text{ALDH}} &= \frac{[\text{fetalaldehyde}^-\text{][NAD}^+]}{[\text{fetalaldehyde}^-\text{][NADH}^+\text{H}^+]} \quad 1.45 \times 10^{-5} \text{ M}^2 \quad 1.45 \times 10^{-9} \quad -0.596 \\
 \text{EC 1.2.1.3} \quad &
 \end{aligned}$$

Cyttoplasmic NADP - Linked Dehydrogenases

$$\begin{aligned}
 4 \bullet 1 \quad K_{\text{ICDH}} &= \frac{[\alpha - \text{KG}^2-\text{][CD}_2^-\text{][NADPH}]}{[\text{l-}\beta\text{-isocitrate}^-\text{][NADP}^+]} \quad 1.17 \text{ M} \quad 1.17 \text{ M} \quad -0.337 \quad -0.472 \quad \text{Here, CO}_2 \text{ is a reactant} \\
 \text{EC 1.1.1.42} \quad & \\
 4 \bullet 2 \quad K_{\text{Malic Enz}} &= \frac{[\text{pyruvate}^-\text{][CD}_2^-\text{][NADPH}]}{[\text{l-}\beta\text{-isocitrate}^-\text{][NADP}^+]} \quad 3.44 \times 10^{-2} \text{ M} \\
 \text{EC 1.1.1.40} \quad & \\
 4 \bullet 3 \quad K_{\text{GPDH}} &= \frac{[\text{ribulose 5-P}^2-\text{][CO}_2^-\text{][NADPH}]}{[\text{6-phosphogluconate}^-\text{][NADP}^+]} \quad 1.72 \times 10^{-1} \text{ M} \\
 \text{EC 1.1.1.43} \quad &
 \end{aligned}$$

* See ref.

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Linking Isomerases

$$4 L 1 \quad K_{60T} = \frac{[\alpha\text{-KG}^{2-}][\text{l-ascorbate}]}{[\text{l-glutamate}][\text{D-galactate}]} \quad 6.61$$

EC 2.6.1.1

$$4 L 2 \quad K_{6PT} = \frac{[\alpha\text{-KG}^{2-}][\text{l-alanine}]}{[\text{l-glutamate}][\text{D-pyruvate}]} \quad 1.52$$

EC 2.6.1.2

$$4 L 3 \quad K_{TP1} = \frac{[\text{dihydroxyacetone-}\beta^{2-}]}{[\text{glyceraldehyde 3-P2-}]} \quad 22$$

EC 5.3.1.1

References for Values of Near-Equilibrium Reactions in Equation 4

Equation Abbreviation Reference

4 C 1 K_{LDH} Williamson DH, Lund P, Krebs HA, *Biochem J* 103: 514-527, 19674 C 2 K_{MDH} Guynn R, Gelberg H, Yeech RL, *J Biol Chem* 246: 6957-6965, 19734 C 3 K_{6PDH} Russell M, Thesis, Munich, 1969.4 C 4 K_{GADH} Cornell M, Leadbetter M, Veetch RL, *J Biol Chem* 254: 6522-6527, 19794 H 1 K_{HBDH} Williamson DH, Lund P, Krebs HA, *Biochem J* 103: 514-527, 19674 H 2 K_{GLDH} Engel P, Dalziel K, *Biochem J* 105: 691-695, 1967

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411	K _{1CDH}	Londesborough J, Dalziel K. <i>Biochem J</i> 110: 217-222, 1968
412	K _{H.E.}	Yeech R, Eggleston LV, Krebs HA. <i>Biochem J</i> 115: 609-619, 1967
413	K _{6PGDH}	Villet R, Dalziel K. <i>Biochem J</i> 115: 633-638, 1969
414	K _{6GT}	Krebs HA. <i>Adv Enz Reg</i> 13: 449-472, 1975
415	K _{6PT}	Krebs HA. <i>Adv Enz Reg</i> 13: 449-472, 1975
416	K _{TPI}	Yeech RL, Rajanah L, Dalziel K, Krebs HA. <i>Biochem J</i> 115: 837-842, 1969

The enzyme aldose reductase EC 1.1.1.21 may be redox active during fructose infusion in certain tissues.
The reaction is:

$$K_{\text{Aldose R}} = \frac{[d\text{-sorbitol}][\text{NADPH}]^+}{[d\text{-glucose}][\text{NAD}^+]}, \quad 2 \times 10^{-11} \text{ M.} \quad \text{My estimate}$$

For description, see Hayano S, Kinoshita JH. *J Biol Chem* 240: 877, 1965

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V Eqn 5 Phosphorylation State Equations - $\frac{[\text{ATP}]}{[\text{ADP}][\text{Pi}]}$

Veech RL, Lawson JR, Cornell NM, Krebs H.H. J Biol Chem 254: 6538-6547, 1979

5a. The equilibrium constant of the glyceraldehyde 3-phosphate dehydrogenase (EC 1.1.1.29) and 3 phosphoglycerate kinase reactions (EC 2.7.2.3) at 38°C, $K = 0.25$, and free $[\text{Mg}^{2+}] = 1 \text{ mM}$ is:

$$K_{6+6} = \frac{[\text{ATP}]}{[\text{GAP}]} \cdot \frac{[\text{NADH}]^4}{[\text{ADP}][\text{Pi}]} \cdot \frac{[\text{NAD}]}{[\text{NADH}]} = 1.03 \times 10^{-4}$$

5b. Combining the above reaction with K_{LDH} and substituting $[\text{DHAP}] = [\text{GAP}] / 22$

$$K_{6+6} \frac{[\text{ATP}]}{[\text{GAP}]} \cdot \frac{[\text{NADH}]}{[\text{NAD}]} \cdot \frac{[\text{l-lactate}]}{[\text{DHAP}]} = 1.03 \times 10^{-4} \cdot \frac{[\text{NADH}]}{[\text{ADP}][\text{Pi}]} \cdot \frac{[\text{pyruvate}]}{[\text{DHAP}]} = 1.65 \times 10^{-7} \text{ M}^{-1}$$

5c. Or:

$$\frac{[\text{ATP}]}{\text{Free Cytoplasmic}} = \frac{[\text{DHAP}]}{[\text{ADP}][\text{Pi}]} \cdot \frac{[\text{pyruvate}]}{[\text{Pi}-\text{lactate}]} \cdot \frac{[\text{pyruvate}]}{7.5 \times 10^{-5} \text{ M}^{-1}}$$

5d. Alternatively, from the creatine phosphokinase reaction (EC 2.7.3.2)

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$$K_{DK} = \frac{[cATP]}{[cADP]} \cdot \frac{[cCreatine]}{[cCreatine-P]H^+} = 1.66 \times 10^{-9} M^{-1}$$

For the Pyrophosphorylation State or [PPi] / [Pi]:

Lawson JWR, Guyton RW, Cornell NW, Veerch RL. In *Gluconeogenesis* (Hanson RW, Mehloian MA eds) pp 481-511, John Wiley, New York, 1976

5e. From the UDPG Pyrophosphorylase reaction (EC 2.7.7.9):

$$\text{Free Cytoplasmic [PPi]} = \frac{[c\text{glucose 1-P}] [c\text{UTP}]}{[c\text{UDPGlucose}]^* K_{\text{UDPGPPiase}}}$$

where $K_{\text{UDPGPPiase}} = 4.55$

5f. For liver and blood glucose:

$$K_{\text{G-PPi Transase}} = \frac{[c\text{Glucose 6-P}] [c\text{Pi}]}{[c\text{Glucose}] [c\text{PPi}]} = 45.9$$

5g.

$$K_{\text{G-PPi Transase}} = \frac{[c\text{free f 1,6 diPi}] [c\text{Pi}]}{[c\text{fructose 6-P}] [c\text{PPi}]} = 29.0$$

VI Eqn 6 Determination of Osmotic Pressure - $\bar{\pi}$

Van't Hoff JH. Arch Nederl Sci 20: 239-303, 1886

$$\bar{\pi} = \Sigma [C] RT$$

where:

 $\bar{\pi}$ ~ osmotic pressure in atmospheres (relative to pure H_2O) $\Sigma [C]$ ~ [concentrations] of solutes in mole/liter R ~ gas constant = 0.082 liter atmospheres/mole/ degree K T ~ $273 + {}^{\circ}C$

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VII Eqn 7 The Equation of State of the Cell

Relating the E across the cell membrane, the distribution of $[Na^+]$, $[K^+]$, $[Cl^-]$, and $[Ca^{2+}]$ between extracellular fluid and cytoplasmic H_2O and hence cell volume to the cytoplasmic $[ATP]/[ADP][Pi]$

$$\Delta G_{Na/K ATPase} = \Delta G_{ATPase} + \Delta G_{ions} + RT \ln \frac{[ATP][Pi]}{[ADP][Cl^-]_i} + RT \ln \frac{[Na^+]_o^3[K^+]_o^2[Cl^-]_o}{[Na^+]_i^3[K^+]_i^2[Cl^-]_i} + TS$$

Since $\Delta G = 0$, then:

$$0 = -7.73 \text{ kcal/mole} + 0 + (-6.3 \text{ kcal/mole}) + 0.5 \text{ kcal/mole} + 5.5 \text{ kcal/mole}$$

$$\text{As 1 kcal/mole} = \frac{0.002 \text{ liter atmose/mole/K}}{1.98 \times 10^{-3} \text{ kcal/mole/K}} \times \frac{1}{22.4 \text{ 1/mole}} = 1.05 \text{ atmospheres}$$

then the TS term = $5.5 \times 1.05 = 10.2$ atmospheres.

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And further from Van't Hoff (Eqn 6)

$$z [C]_{in} - z [C]_{out} = \frac{2}{RT}$$

$$z [C]_{in} - z [C]_{out} = 0.40 \text{ moles/L}$$

Eqn 7 states that since H_2O outside = H_2O inside, the cell is prevented from swelling by the Na^+/K^+ ATPase which electroreutrally pumps out 2 ~~moles~~ ATP hydrolysed. The ΔE across the cell (membrane) is reflected by the distribution of $[\text{Cl}^-]_0 / [\text{Cl}^-]_i$ in accordance with the Nernst equation (Eqn 3). The ΔS or decreased entropy within the living cell represents the increase "order" characteristic of the living cell. See Eqn 9.

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1 7b. From the high capacity $\text{Na}^+/\text{Ca}^{2+}$ exchanger written in
an electroneutral manner reflecting the free permeability
of Cl^- in accordance with the dictates of the Nernst
equation, (Eqn 3):

5 $3 \text{Na}^+_o + \text{Ca}^{2+}_i + \text{Cl}^-_o \rightleftharpoons 3 \text{Na}^+_i + \text{Ca}^{2+}_o + \text{Cl}^-_i$;
The net osmolar movement of eqn 7a is 2 osmoles \rightarrow
outside. In contrast, the net movement of eqn 7b is 3
osmoles \rightarrow inside, requiring the Na^+/K^+ ATPase to cycle
3 times for each 2 times the $\text{Na}^+/\text{Ca}^{2+}$ exchange mechanism
10 operates in order to maintain osmotic equilibrium.

The gradient $[\text{Ca}^{2+}]_i / [\text{Ca}^{2+}]_o$ is thus a direct
function of the $[\text{Na}^+]_o^3 / [\text{Na}^+]_i^3$, (the $[\text{Cl}^-]_o / [\text{Cl}^-]_i$),
and a function of the phosphorylation and entropy state
of the cell.

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1 It will be clear to those skilled in the art
that equation 7 is the statement of the reaction which
links the external environment of the cell to its
internal environment and metabolic machinery.

5 Extracellular fluid is thus a creation of the metabolic
process of the cell. Changing the external $[Na^+]$,
 $[K^+]$, $[Cl^-]$, or $[Ca^{2+}]$, or the $[H_2O]$ must necessarily
effect the same parameters inside the cell.

10 Additionally, the redox and phosphorylation
states, the ΔE , and the $T\Delta S$ of the cell are all
related and therefore manipulable by the relationships
given.

15 To control these parameters one needs to use
solutions as provided herein which include defined
concentrations of Na^+ , K^+ , Cl^- and Ca^{2+} and the
related ions HCO_3^- , H^+ , at a defined Mg^{2+} concentration
and with a defined osmotic pressure.

Thus, the present invention provides a process
for regulating:

20 1) Distribution of water between intracellular
and extracellular fluid.

2) Distribution of the inorganic electrolytes
 Na , K , Cl and Ca between intracellular
and extracellular fluid.

25 3) and transmembrane cellular potential

This process is practiced by contacting cells with
aqueous near-equilibrium couples as taught by this
inventor or by varying the external concentration of
 Na^+ , K^+ , Cl^- or Ca^{2+} . For example a solution with low
30 $Na:Cl$ ratio raises the phosphorylation potential (See
Table III above). In other circumstances, raising
 $Na:Cl$ outside may raise cellular $[Ca^{2+}]$ for example in
rat liver.

Having now fully described the invention, it will
35 be apparent to one of ordinary skill in the art that

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1 many changes and modifications can be made thereto without departing from the spirit or scope of the invention as set forth herein.

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1 CLAIMS

1. An in vivo process which (a) tends to maintain the normal plasma milliequivalent ratio of sodium cations to chloride anions in a normal range and (b) tends to 5 maintain normal plasma and cellular pH, and (c) tends to maintain normal cellular cofactor ratios, said process comprising introducing within a living mammal a physiologically effective amount of an aqueous solution comprising water which has dissolved therein:

10 (A) at least one of the following near equilibrium couples in the respective quantities indicated:

(1) from 0 to about 465 millimoles per liter of a first couple mixture consisting of bicarbonate anions and carbon dioxide wherein the milliequivalent ratio of said bicarbonate anions to said carbon dioxide ranges from about 0.1:1 to 55:0.1,

15 (2) from 0 to about 465 millimoles per liter of a second couple mixture consisting of l-lactate anions and pyruvate anions wherein the milliequivalent ratio of said l-lactate anions to said pyruvate anions ranges from about 20:1 to 1:1,

20 (3) from about 0 to about 465 millimoles per liter of a third couple mixture consisting of d-betahydroxybutyrate to said acetoacetate anions wherein the milliequivalent ratio of said d-betahydroxybutyrate to said acetoacetate ranges from about 6:1 to 0.5:1,

25 (B) from about 1 to 2400 millimoles per liter of sodium cations,

(C) sufficient millimoles per liter of chloride anions to produce a milliequivalent ratio of sodium cations to chloride anions in the range from about 1.24 to 1.6,

30

35

1 (D) optionally from 0 to about 2400 millimoles per liter of at least one osmotically active substantially nonionic substance,
5 (E) optionally at least one of the following additional cations in a respective quantity as indicated:

<u>cation</u>	<u>quantity</u> (in millimoles/liter)
potassium	0 - 90
calcium	0 - 60
magnesium	0 - 15

10 the relationship between said water and all solutes in said water being such that said solution is characterized by having:

15 (1) an osmolarity ranging from about 250 to 5000 milliosmoles;
(2) a pH in the range from about 5 to 9;
(3) the charges of all cations equal the charges of all anions; and
20 (4) the minimum total concentration of all said near equilibrium couples present in said solution is at least about 0.1 millimole per liter.

25 2. A physiologically compatible aqueous salt solution for mammalian administration which (a) tends to maintain a normal plasma milliequivalent ratio of sodium cations to chloride anions in a normal range, and (b) tends to maintain normal plasma and cellular pH and tends to maintain normal cellular co-factor ratios, said solution comprising water which has dissolved therein:

30 (A) at least one of the following near equilibrium couples in the respective quantities indicated:
35 (1) from 0 to about 465 millimoles per liter of a first couple mixture consisting of bicarbonate anions and carbon dioxide wherein the milliequivalent ratio of said bicarbonate anions to said carbon dioxide ranges from about 0.1:1 to 55:0.1,

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1 (2) from 0 to about 465 millimoles per liter
of a second couple mixture consisting of
1-lactate anions and pyruvate anions
wherein the milliequivalent ratio of said
1-lactate anions to said pyruvate anions
ranges from about 20:1 to 1:1,
5 (3) from about 0 to about 465 millimoles per
liter of a third couple mixture consisting
of d-betahydroxybutyrate anions and
acetoacetate anions wherein the milli-
equivalent ratio of said d-betahydroxy-
butyrate to said acetoacetate ranges from
10 about 6:1 to 0.5:1,
15 (B) from about 1 to 2400 millimoles per liter of
sodium cations,
(C) sufficient millimoles per liter of chloride
anions to produce a milliequivalent ratio of
sodium cations to chloride anions in the range
from about 1.24 to 1.6,
20 (D) optionally from 0 to about 2400 millimoles per
liter of at least one osmotically active
substance,
(E) optionally at least one of the following
additional cations in a respective quantity
as indicated:
25

quantity

cation.

(in millimoles/liter)

potassium

0 - 90

calcium

0 - 60

magnesium

0 - 15

- (F) optionally from 0 to about 25 millimoles per liter of sigma inorganic phosphate,
- (G) optionally from 0 to about 2 millimoles per liter of sigma inorganic sulfate,

35 the relationship between said water and all solutes in said water being such that said solution is characterized by having:

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1 (1) an osmolarity ranging from about 260 to 5000 milliosmoles;

5 (2) a pH in the range from about 5 to 9;

(3) the charges of all cations equal the charges of all anions; and

(4) the minimum total concentration of all said near equilibrium couples present in said solution is at least about 0.1 millimoles per liter.

10 3. The solution of claim 2 additionally containing

(a) optionally from 0 to about 25 millimoles per liter of sigma inorganic phosphate, and

(b) optionally from 0 to about 2 millimoles per liter of sigma inorganic sulfate.

15 4. The solution of claim 2 wherein, of each of said first, said second, and said third couple mixtures, a combination of said first couple mixture plus at least one of either of said second couple mixtures or of said 20 third couple mixture is employed, and whereby both normalization of cellular co-factor ratios and normalization of both plasma and intracellular fluid pH tends to be achieved.

25 5. The solution of claim 2 wherein said nonionic substance is metabolizable and the amount thereof ranges from 0 to about 15 millimoles per liter of at least one dissolved metabolizable nonionic osmotically active substance in said solution is such as to produce a milliosmolarity therein in the range from about 280 to 30 320.

6. The solution of claim 5 wherein said nonionic substance comprises glucose.

7. The solution of claim 5 wherein said nonionic substance is selected from the group consisting of glucose 35 fructose, glycerol, and sorbitol.

1 8. The solution of claim 2 wherein at least one of said second and said third couple mixtures is employed.

9. The solution of claim 8 wherein only said second couple mixture is employed.

5 10. The solution of claim 8 wherein only said third couple mixture is employed.

11. The solution of claim 8 wherein said first couple mixture is additionally present.

10 12. The solution of claim 2 wherein each of said first, said second, and said third couple mixtures are all employed.

13. The solution of claim 4 wherein said carbon dioxide is produced in situ by including in said solution a dissolved mixture of

15 (A) at least one member of the group consisting of physiologically acceptable bicarbonate salts, and

20 (B) at least one carboxylic acid selected from the group consisting of l-lactic acid, pyruvic acid, d-betahydroxybutyric acid, and acetoacetic acid,

and provided that:

(a) the total molar quantity of said carboxylic acid and the total molar quantity of said bicarbonate salts is such 25 that there is produced in said solution a quantity of dissolved carbon dioxide sufficient to make said mole ratio of said bicarbonate anions to said carbon dioxide fall in within said range, and

30 (b) the total quantity of all bicarbonate anions remains within a value such that said mole ratio of said bicarbonate anions in said solution to said carbon dioxide falls within said range, and

35 (c) the total individual quantities of said respective carboxylic acids is such that said mole ratio of l-lactate to pyruvate, and said mole ratio of d-betahydroxybutyrate to acetoacetate each remain within said respective ranges.

14. The solution of claim 2 wherein said mole ratio of said bicarbonate anions to said carbon dioxide ranges from about 0.1:1 to 55:0.1.

1 15. The solution of claim 2 wherein substantially the only cation present is sodium.

16. The solution of claim 2 which contains not more than two cations one of which is said sodium while 5 the other thereof is selected from the group consisting of potassium, magnesium, and calcium.

17. The solution of claim 2 which contains three cations, one of which is sodium while the others thereof are selected from the group consisting of potassium, 10 magnesium, and calcium.

18. The solution of claim 17 wherein said three cations are sodium, potassium and calcium.

19. The solution of claim 2 which contains all four of said cations sodium, potassium, magnesium, and 15 calcium.

20. An in vivo process for accomplishing electrolyte and fluid therapy which (a) tends to maintain the normal plasma milliequivalent ratio of sodium cations to chloride anions in a normal range, and (b) tends to maintain 20 normal plasma and cellular pH, and (c) tends to maintain normal cellular co-factor ratios, said process comprising introducing intravenously into a mammal at a physiologically effective rate an aqueous solution comprising water which has dissolved therein each of the following components in 25 the respective amounts indicated:

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1	Component	Quantity Range (millimoles per liter)
	Total cations (mEq/L)	1 to about 2400
	(1) sodium ⁺	1 to about 2400
5	(2) potassium ⁺	0 to about 90
	(3) calcium ⁺⁺	0 to about 60
	(4) magnesium ⁺⁺	0 to about 15
	Total anions (mEq/L)	1 to about 2400
	(5) chloride ⁻	0.6 to about 1940
10	(6) bicarbonate ⁻	0 to about 465
	(7) l-lactate ⁻ and pyruvate ⁻	0 to about 465
	(8) d-betahydroxybutyrate ⁻ and acetoacetate ⁻	0 to about 465
	(9) sum (6, 7, and 8)	0.4 to about 465
15	Total nonionics	0 to about 2400
	(10) carbon dioxide	0 to about 25
	(11) osmotically active substances	0 to about 2400
	the relationship between said water and said components being such that the following always holds:	
20	(12) the milliequivalent ratio of $\text{HCO}_3^-/\text{CO}_2$ ranges from about 0.1/1 to 55/0.1;	
	(13) the milliequivalent ratio of l-lactate ⁻ /pyruvate ⁻ ranges from about 20/1 to 1/1;	
	(14) the milliequivalent ratio of d-betahydroxybutyrate ⁻ / acetoacetate ⁻ ranges from about 6/1 to 0.5/1;	
25	(15) the milliequivalent ratio of Na:Cl ranges from about 1.24 to 1.6;	
	(16) the milliosmoles/L ranges from about 260 to 5000; and	
	(17) the solution pH ranges from about 5 to 9.	
30	21. A physiologically compatible aqueous salt solution for mammalian administration to accomplish electrolyte and fluid therapy, which (a) tends to maintain a normal plasma milliequivalent ratio of sodium cations to chloride anions, (b) tends to maintain normal plasma 35 and cellular pH, and (c) tends to maintain normal cellular co-factor ratios, said solution comprising water which has dissolved therein each of, the following components in the respective amounts indicated:	

SUBSTITUTE SHEET

1	Component	Quantity Range (millimoles per liter)
	Total Cations (mEq/L)	1 to about 2400
5	(1) sodium ⁺	1 to about 2400
	(2) potassium ⁺	0 to about 90
	(3) calcium ⁺⁺	0 to about 60
	(4) magnesium ⁺⁺	0 to about 15
	Total Anions (mEq/L)	1 to about 2400
	(5) chloride ⁻	0.6 to about 1940
10	(6) bicarbonate ⁻	0 to about 465
	(7) l-lactate ⁻ and pyruvate ⁻	0 to about 465
	(8) d-betahydroxybutyrate ⁻ and acetoacetate ⁻	0 to about 465
	(9) sum (6, 7 and 8)	0.4 to about 465
15	Total nonionics	0 to about 2400
	(10) carbon dioxide	0 to about 25
	(11) osmotically active substances	0 to about 2400
	the relationship between said water and said components being such that the following always holds:	
20	(12) the milliequivalent ratio of $\text{HCO}_3^-/\text{CO}_2$ ranges from about 0.1/1 to 55/0.1;	
	(13) the milliequivalent ratio of l-lactate ⁻ /pyruvate ⁻ ranges from about 20/1 to 1/1;	
	(14) the milliequivalent ratio of d-betahydroxybutyrate ⁻ / acetoacetate ⁻ ranges from about 6/1 to 0.5/1;	
25	(15) the milliequivalent ratio of Na:Cl ranges from about 1.24 to 1.6;	
	(16) the milliosmolarity ranges from about 260 to 5000; and	
30	(17) the solution pH ranges from about 5 to 9.	

22. An in vivo process which (a) tends to maintain the normal plasma milliequivalent ratio of sodium cation to chloride anions in a normal range, and (b) tends to maintain normal cellular co-factor ratios and/or tends to normalize plasma pH, and (c) accomplishes electrolyte and fluid and resuscitation therapy said process comprising intravascularly introducing into blood of a mammal a physiologically effective amount but not more than about

1 1 liter per 70 kilogram of mammal body weight per day an aqueous solution comprising water which has dissolved therein each of the following components in the respective quantities indicated:

5	Quantity Range
	(millimoles per liter)
Component	
Total cations (mEq/L)	1 to about 170
(1) sodium ⁺	1 to about 170
(2) potassium ⁺	0 to about 10
10 (3) calcium ⁺⁺	0 to about 5
(4) magnesium ⁺⁺	0 to about 5
Total anions (mEq/L)	1 to about 170
(5) chloride ⁻	0.6 to about 137
(6) bicarbonate ⁻	0 to about 64
15 (7) l-lactate ⁻ + pyruvate ⁻	0 to about 64
(8) d-betahydroxybutyrate ⁻ + acetoacetate ⁻	0 to about 64
(9) sum (6, 7 and 8)	0.4 to about 64
Total nonionics	0 to about 625
20 (10) carbon dioxide	0 to about 25
(11) osmotically active substances	0 to about 600
the relationship between said water and said components being such that the following relationships always hold:	
25 (12) the milliequivalent ratio of $\text{HCO}_3^-/\text{CO}_2$ ranges from about 0.1/1 to 55/0.1;	
(13) the milliequivalent ratio of l-lactate ⁻ /pyruvate ⁻ ranges from about 20/1 to 1/1;	
(14) the milliequivalent ratio of d-betahydroxybutyrate ⁻ /acetoacetate ⁻ ranges from about 6/1 to 0.5/1;	
30 (15) the milliequivalent ratio of Na:Cl ranges from about 1.24 to 1.6;	
(16) the milliosmoles/L ranges from about 240 to 950; and	
(17) the solution pH ranges from about 5 to 9.	

1 23. A physiologically compatible aqueous salt
 solution for mammalian administration to accomplish
 electrolyte, fluid and resuscitation therapy which (a)
 tends to maintain the normal plasma milliequivalent
 5 ratio of sodium cations to chloride anions in a normal
 range (b) tends to maintain normal plasma and cellular
 pH, and (c) tends to maintain normal cellular co-factor
 ratios, said solution comprising water which has dissolved
 therein each of the following components in the respective
 10 amounts indicated:

Component	Quantity Range (millimoles per liter)
Total cations (mEq/L)	1 to about 170
(1) sodium ⁺	1 to about 170
(2) potassium ⁺	0 to about 10
(3) calcium ⁺⁺	0 to about 5
(4) magnesium ⁺⁺	0 to about 5
Total anions (mEq/L)	1 to about 170
(5) chloride ⁻	0.6 to about 137
(6) bicarbonate ⁻	0 to about 64
(7) l-lactate ⁻ + pyruvate ⁻	0 to about 64
(8) d-betahydroxybutyrate ⁻ + acetoacetate ⁻	0 to about 64
(9) sum (6, 7 and 8)	0.4 to about 64
Total nonionics	0 to about 625
(10) carbon dioxide	0 to about 25
(11) osmotically active substances	0 to about 600
the relationship between said water and said components being such that the following relationships always hold:	
(12) the milliequivalent ratio of $\text{HCO}_3^-/\text{CO}_2$ ranges from about 0.1/1 to 55/0.1;	
(13) the milliequivalent ratio of l-lactate ⁻ /pyruvate ⁻ ranges from about 20/1 to 1/1;	
(14) the milliequivalent ratio of d-betahydroxybutyrate ⁻ / acetoacetate ⁻ ranges from about 6/1 to 0.5/1;	
(15) the milliequivalent ratio of Na:Cl ranges from about 1.24 to 1.6;	
(16) the milliosmoles/L ranges from about 240 to 950;	
(17) the solution pH ranges from about 5 to 9.	

1 24. A dialysis fluid for mammalian administration
 which (a) tends to maintain a normal plasma milliequivalent
 ratio of sodium cations to chloride anions, (b) tends to
 maintain normal plasma and cellular pH, and (c) tends to
 5 maintain normal cellular co-factor ratios, said fluid
 comprising water which has dissolved therein each of the
 following components in the respective amounts indicated:

		Quantity Range (millimoles per liter)
10	Component	
10	Total cations (mEq/L)	about 130 to 170
	(1) sodium ⁺	about 130 to 155
	(2) potassium ⁺	0 to about 6
	(3) calcium ⁺⁺	0 to about 3
	(4) magnesium ⁺⁺	0 to about 2
15	Total anions (mEq/L)	about 130 to 170
	(5) chloride ⁻	about 81 to 125
	(6) bicarbonate ⁻	0 to about 60
	(7) l-lactate ⁻ plus pyruvate ⁻	0 to about 60
	(8) d-betahydroxybutyrate ⁻ plus acetoacetate ⁻	0 to about 60
20	(9) sum (6+7+8)	about 25 to 60
	Total nonionics	0 to about 525
	(10) carbon dioxide	0 to about 25
	(11) osmotically active substances	0 to about 500
25	the relationship between said water and said components being such that:	
	(12) the milliequivalent ratio of $\text{HCO}_3^-/\text{CO}_2$ ranges from about 0.1/1 to 55/0.1;	
	(13) the milliequivalent ratio of l-lactate ⁻ /pyruvate ⁻ ranges from about 20/1 to 1/1;	
30	(14) the milliequivalent ratio of d-betahydroxybutyrate ⁻ / acetoacetate ⁻ ranges from about 6/1 to 0.5/1;	
	(15) the milliequivalent ratio of Na:Cl ranges from about 1.24 to 1.6;	
35	(16) the milliosmolarity ranges from about 260 to 850, and	
	(17) the solution pH ranges from about 5 to 9.	

1 25. In a hemodialysis process fo the type where
renal function of a living mammal is replaced at least
in part by dialysis and wherein portions of the blood of
said mammal are continuously passed over one face of a
5 dialysis membrane which the opposed face of said dialysis
membrane is contacted with a dialysis fluid, thereby
to achieve a change in the chemical composition of the
body fluids, and wherein said dialysis fluid contains
dissolved therein the same principal inorganic electro-
10 lytes at respective individual concentration levels to
approximating those found in the plasma or serum of
normal mammals of the same species, the improvement which
comprises using as said dialysis fluid an aqueous solution
which has dissolved therein each of the following com-
15 ponents in the respective amounts indicated:

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1	Component	Quantity range (millimoles per liter)
	Total cations (mEq/L)	about 130 to 170
5	(1) sodium ⁺	about 130 to 155
	(2) potassium ⁺	0 to about 5
	(3) calcium ⁺⁺	0 to about 3
	(4) magnesium ⁺⁺	0 to about 2
	Total anions (mEq/L)	about 130 to 170
10	(5) chloride ⁻	about 84 to 125
	(6) bicarbonate ⁻	about 0 to 55
	(7) l-lactate ⁻ and pyruvate ⁻	about 0 to 55
	(8) d-betahydroxybutyrate ⁻ and acetoacetate ⁻	about 0 to 55
	(9) sum (6+7+8)	about 25 to 55
15	Total nonionics	0 to about 525
	(10) carbon dioxide	0 to about 25
	(11) osmotically active substance	0 to about 500
	the relationship between said water and said components always being such that:	
20	(12) mEq. ratio of bicarbonate ⁻ /CO ₂ ranges from about 0.1/l to 55/0.1;	
	(13) mEq. ratio of l-lactate ⁻ /pyruvate ⁻ ranges from about 20/l to 1/l;	
	(14) mEq. ratio of d-betahydroxybutyrate ⁻ /acetoacetate ⁻ ranges from about 6/l to 0.5/l;	
25	(15) mEq. ratio of Na:Cl ranges from about 1.24 to 1.6	
	(16) milliosmoles/L ranges from about 260 to 800;	
	(17) pH of solution ranges from about 5 to 9.	
	26. A hemodialysis fluid for mammalian administration which (a) tends to maintain a normal plasma milliequi-	
30	valent ratio of sodium cations to chloride anions and (b) tends to maintain normal plasma and cellular pH and (c) tends to maintain normal cellular co-factor ratios, said fluid comprising water which has dissolved therein each of the following components in the respective amounts	
35	indicated:	

		Quantity Range (millimoles per liter)
Component		
1	Total cations (mEq/L)	about 130 to 170
5	(1) sodium ⁺	about 130 to 155
5	(2) potassium ⁺	0 to about 5
5	(3) calcium ⁺⁺	0 to about 3
5	(4) magnesium ⁺⁺	0 to about 2
10	Total anions (mEq/L)	about 130 to 170
10	(5) chloride ⁻	about 84 to 125
10	(6) bicarbonate ⁻	about 0 to 55
10	(7) l-lactate ⁻ and pyruvate ⁻	about 0 to 55
10	(8) d-betahydroxybutyrate ⁻ and acetoacetate ⁻	about 0 to 55
15	(9) sum (6+7+8)	about 25 to 55
15	Total nonionics	0 to about 525
15	(10) carbon dioxide	0 to about 25
15	(11) osmotically active substance	0 to about 500
20	the relationship between said water and said components always being such that:	
20	(12) mEq. ratio of bicarbonate ⁻ /CO ₂ ranges from about 0.1/1 to 55/0.1;	
20	(13) mEq. ratio of l-lactate ⁻ /pyruvate ⁻ ranges from about 20/1 to 1/1;	
25	(14) mEq. ratio of d-betahydroxybutyrate ⁻ /acetoacetate ⁻ range from about 6/1 to 0.5/1;	
25	(15) mEq. ratio of Na:Cl ranges from about 1.24 to 1.6;	
25	(16) milliosmoles/L ranges from about 260 to 800;	
25	(17) pH of solution ranges from about 5 to 9.	

27. In a process of the type where renal function
30 of a living mammal is replaced at least in part by
dialysis and wherein a dialysis fluid is charged into the
peritoneal cavity of such mammal for a time sufficient
to achieve a change in the chemical composition of the
body fluids, and wherein said dialysis fluid contains
35 dissolved therein the same principal inorganic electro-
lytes at respective individual concentration levels
approximately those found in the plasma or serum of
normal mammals of the same species, the improvement

1 which comprises accomplishing simultaneously with such
 dialysis (a) the maintenance of a normal plasma milli-
 equivalent ratio of sodium cations to chloride anions,
 (b) the maintenance of normal plasma and cellular pH,
 5 and (c) tends to maintain normal cellular co-factor
 ratios, such improvement being achieved by employing
 as said dialysis fluid an aqueous solution which has
 dissolved therein each of the following components in the
 respective amounts indicated:

		Quantity Range (millimoles per liter)
10	<u>Component</u>	
	Total cations (mEq/L)	about 130 to 170
	(1) sodium ⁺	about 130 to 165
15	(2) potassium ⁺	0 to about 5
	(3) calcium ⁺⁺	0 to about 2
	(4) magnesium ⁺⁺	0 to about 1.5
	Total anions (mEq/L)	about 130 to 170
	(5) chloride ⁻	about 81 to 130
20	(6) bicarbonate ⁻	0 to about 55
	(7) l-lactate ⁻ and pyruvate ⁻	0 to about 55
	(8) d-betahydroxybutyrate ⁻ and acetoacetate ⁻	0 to about 55
	(9) sum (6+7+8)	about 26 to 55
25	Total nonionics	about 40 to 252
	(10) carbon dioxide	about 0 to 25
	(11) osmotically active substance	about 40 to 250
	the relationship between said water and said components always being such that:	
30	(12) the milliequivalent ratio of $\text{HCO}_3^-/\text{CO}_2$ ranges from about 0.1/l to 160/l;	
	(13) the milliequivalent ratio of l-lactate ⁻ /pyruvate ⁻ ranges from about 20/l to 1/l;	
	(14) the milliequivalent ratio of d-betahydroxybutyrate ⁻ / acetoacetate ⁻ ranges from about 6/l to 0.5/l;	
35	(15) the milliequivalent ratio of Na:Cl ranges from about 1.24 to 1.6;	
	(16) the milliosmolarity per liter ranges from about 311 to 615 and	

1 (17) the solution pH ranges from about 5 to 8.

28. A peritoneal dialysis fluid for mammalian administration which (a) tends to maintain a normal plasma milliequivalent ratio of sodium cations to chloride anions, (b) tends to maintain normal plasma and cellular pH, and (c) tends to maintain normal cellular co-factor ratios, said fluid comprising water which has dissolved therein each of the following components in the respective amounts indicated:

		Quantity Range (millimoles per liter)
10	Component	
	Total cations (mEq/L)	about 130 to 170
15	(1) sodium ⁺	about 130 to 165
	(2) potassium ⁺	0 to about 5
	(3) calcium ⁺⁺	0 to about 2
	(4) magnesium ⁺⁺	0 to about 1.5
20	Total anions (mEq/L)	about 130 to 170
	(5) chloride ⁻	about 81 to 130
	(6) bicarbonate ⁻	0 to about 55
	(7) l-lactate ⁻ and pyruvate ⁻	0 to about 55
	(8) d-betahydroxybutyrate ⁻ and acetoacetate ⁻	0 to about 55
	(9) sum (6+7+8)	about 26 to 55
25	Total nonionics	about 40 to 252
	(10) carbon dioxide	about 0 to 25
	(11) osmotically active substance	about 40 to 250
	the relationship between said water and said components always being such that:	
30	(12) the milliequivalent ratio of $\text{HCO}_3^-/\text{CO}_2$ ranges from about 0.1/1 to 160/1;	
	(13) the milliequivalent ratio of l-lactate ⁻ /pyruvate ⁻ ranges from about 20/1 to 1/1;	
	(14) the milliequivalent ratio of d-betahydroxybutyrate ⁻ /acetoacetate ⁻ ranges from about 6/1 to 0.5/1;	
35	(15) the milliequivalent ratio of Na:Cl ranges from about 1.24 to 1.6;	
	(16) the milliosmolarity per liter ranges from about 311 to 615, and	

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1 (17) the solution pH ranges from about 5 to 8.

29. A process for regulating:

(1) distribution of water between intra-cellular and extracellular fluid,

5 (2) distribution of the inorganic electrolytes Na, K, Cl, Ca between intracellular and extracellular fluid,

(3) transmembrane cellular potential,

comprising contacting a living animal cell with an aqueous 10 solution comprising water which has dissolved therein:

(A) at least one of the following near equilibrium couples in the respective quantities indicated:

(1) from 0 to about 465 millimoles per liter of a first couple mixture consisting of bicarbonate anions and carbon dioxide wherein the milli-equivalent ratio of said bicarbonate anions to said carbon dioxide anions ranges from 0.1:1 to 55:0.1,

20 (2) from 0 to about 465 millimoles per liter of a second couple mixture consisting of l-lactate anions and pyruvate anions wherein the milli-equivalent ratio of said l-lactate anions to said pyruvate anions ranges from about 20:1 to 1:1;

25 (3) from about 0 to about 465 millimoles per liter of a third couple mixture consisting of d-betahydroxybutyrate anions and acetoacetate anions wherein the milliequivalent ratio of said d-betahydroxybutyrate to said acetoacetate ranges from about 6:1 to 0.5:1,

30 (B) from about 1 to 2400 millimoles per liter of sodium cations,

35 (C) sufficient millimoles per liter of chloride anions to produce a milliequivalent ratio of sodium cations to chloride anions in the range from 1.24 to 1.6,

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1 (D) optionally from 0 to about 2400 millimoles per liter of at least one osmotically active substantially nonionic substance,

5 (E) the following additional cations in the respective quantities indicated:

Cation	Quantity (in millimoles/liter)
potassium	0 - 90
calcium	0 - 60
10 magnesium	0 - 15

the relationship between said water and all solutes in said water being such that said solution is characterized by having:

15 (1) an osmolarity ranging from about 260 to 5000 milliosmoles/liter;

(2) a pH in the range from about 5 to 9;

(3) the charges of all cations equal the charges of all anions, and

(4) the minimum total concentration of all said near equilibrium couples(s) present in said solution is at least about 0.1 millimole per liter.

20 30. A process for effecting in a living cell simultaneously each of:

25 (A) the redox state, $[NAD^+]/[NADH]$ or $[NADP^+]/[NADPH]$;

(B) the phosphorylation potential, $[\Sigma ATP]/[\Sigma ADP][\Sigma Pi]$

(C) the distribution of H_2O between extra-cellular and intracellular space

30 (D) the E , (transmembrane potential) and

(E) the $T S$ (an energy term)

by contracting such cell with an aqueous solution comprising water which has dissolved therein:

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1 (A) at least one of the following near equi-librium couples in the respective quantities indicated:

5 (1) from 0 to about 465 millimoles per liter of a first couple mixture consisting of bicarbonate anions and carbon dioxide wherein the milliequivalent ratio of said bicarbonate anions to said carbon dioxide ranges from about 0.1:1 to 55:0.1,

10 (2) from 0 to about 465 millimoles per liter of a second couple mixture consisting of l-lactate anions and pyruvate anions wherein the milliequivalent ratio of said l-lactate anions to pyruvate anions ranges from about 20:1 to 1:1,

15 (3) from 0 to about 465 millimoles per liter of a third couple consisting of d-betahydroxybutyrate anions and acetoacetate anions wherein the milliequivalent ratio of said d-betahydroxybutyrate to said acetoacetate ranges from about 6:1 to 0.5:1,

20 (B) from about 1 to 2400 millimoles per liter of sodium cations;

25 (C) sufficient millimoles per liter of chloride anions to produce a milliequivalent ratio of sodium cations to chloride anions in the range from about 1.24 to 1.6.

30 (D) optionally from 0 to about 2400 millimoles per liter of at least one osmotically active substance,

35 (E) the following additional cations in the respective quantities indicated:

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	Quantity (in millimoles/liter)
1	Cations
	potassium 0 - 90
	calcium 0 - 60
5	magnesium 0 - 15
	the relationship between said water and all solutes in said water being such that said solution is characterized by having:
10	(1) an osmolarity ranging from about 260 to 5000 milliosmoles per liter;
	(2) a pH in the range from about 5 to 9;
	(3) the charges of all cations equal the charges of all anions, and
15	(4) the minimum total concentration of all said near equilibrium couples present in said solution is at least about 0.1 millimole per liter.

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INTERNATIONAL SEARCH REPORT

International Application No.

PCT/US85/01202

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate any \pm)

According to International Patent Classification (IPC) or to both National Classification and IPC

INT CL 4 A61K 31/56, 31/65, 31/66 and 31/70

II. FIELDS SEARCHED

Minimum Documentation Searched \downarrow

Classification System	Classification Symbols
US	424-146, 153 + 180 514-23

Documentation Searched other than Minimum Documentation
to the Extent that such Documents are Included in the Fields Searched \downarrow

III. DOCUMENTS CONSIDERED TO BE RELEVANT \downarrow

Category \downarrow	Citation of Document, \downarrow with indication, where appropriate, of the relevant passages \downarrow	Relevant to Claim No. \downarrow
X	U.S. 3,970,750, Pub. 20 July 1976 Brockemeyer et al	ALL
X	U.S. 3,993,750, Pub. 23 Nov 1976 FOX, Jr. et al	ALL
X	Physicians' Desk Reference, 28th Ed. (1974), p. 1257	ALL

• Special categories of cited documents: \downarrow

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
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- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

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"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search \downarrow

09 Sept. 1985

Date of Mailing of this International Search Report \downarrow

04 OCT 1985

International Searching Authority \downarrow

USA/US

Signature of Authorized Officer \downarrow

Stanley J. Friedman

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